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(54) Title: ACTIVIN RECEPTOR-LIKE KINASES, PROTEINS HAVING SERINE THREONINE KINASE DOMAINS AND THEIR USE

cons.aa	G G	G V	A K	E
hTGFBR-II	LDTLVCKGRFAEVYTKLQNTSEQFETVAVKIFPYDHYASWKRKDIFSDINLKHENILQF			
mActR-II B	LLEIKARGRFCCVWKAQLLN-----DFVAVKIKPLQDKQSWSQSEREIFSTPGMKHENILQF			
mActR-II	LLEVKARGRGFCVWKAQLLN-----EYVAVKIFPTIQDKQSWSQNEYEVYSIPTGMKHENILQF			
daf-1	LGRVGSGRFGNVSRGDYR-----EAVAVKVFNAIDEPAPHKEIEIFPETRMLRHPNVILY			
subdomains	I	II	III	IV

hTGFBR-II	LTAEEKRTELGKQYWLITAFHAKGNLQEYLTRHVI SWEDLRNVGSSLARGLSHLHSDFHTP-C			
mActR-II B	IAAEKRGSNLEVELWLITAFHDKGSLSIDYLGKNI ITWNELCHVAETMSRGISYIHLEDWPWCR			
mActR-II	IGAEKRGTSVVDVILWLITAFHDKGSLSDFLKEANVSWNELCHIAETMARGLAVLHEDIPGLK			
daf-1	IGSDRVIDTGFVTELWLVIEYHPSGSILHDFFLLENVNIETYNNLMRSTASGLAFLHNQIGGSK			
subdomains	V	VI	VII	VIII

cons.aa	DLK N	DFG	
hTGFBR-II	-GRPKMPIVHRLDKSSNIVLVRNDLTCCLCDFGLSLRL--GPYSSVDDLANSQVGVTARYMAP		
mActR-II B	GEGHKPSIAHDFKSKNVLLKSDLTAVLADFGLAVERF--EPGKPPGD--THGQVGTRRYMAP		
mActR-II	-DGHKPAISHRDIKSKNVLLKNNLTACIADFGLALKF--EAGKSAGD--THGQVGTRRYMAP		
daf-1	-ESNKPAMAHDIYSKINMVKNDLTCAIGDGLGLSLSKPVEDAASIIAN-ENYKCGTVRYLAP		
subdomains	VI-B	VII	VIII

(57) Abstract

A new receptor family has been identified, of activin-like kinases. Novel proteins have activin/TGF- β -type I receptor functionality, and have consequential diagnostic/therapeutic utility. They may have a serine/threonine kinase domain, a DFKSRN or DLKSKN sequence in subdomain VIB and/or a GTKRYM sequence in subdomain VIII.

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ACTIVIN RECEPTOR-LIKE KINASES, PROTEINS HAVING
SERINE THREONINE KINASE DOMAINS AND THEIR USE.

Field of the Invention

This invention relates to proteins having
5 serine/threonine kinase domains, corresponding nucleic acid
molecules, and their use.

Background of the Invention

The transforming growth factor- β (TGF- β) superfamily
consists of a family of structurally-related proteins,
10 including three different mammalian isoforms of TGF- β (TGF- β 1, β 2 and β 3), activins, inhibins, müllerian-inhibiting
substance and bone morphogenic proteins (BMPs) (for reviews
see Roberts and Sporn, (1990) Peptide Growth Factors and
Their Receptors, Pt.1, Sporn and Roberts, eds. (Berlin:
15 Springer - Verlag) pp 419-472; Moses *et al* (1990) Cell 63,
245-247). The proteins of the TGF- β superfamily have a
wide variety of biological activities. TGF- β acts as a
growth inhibitor for many cell types and appears to play a
central role in the regulation of embryonic development,
20 tissue regeneration, immuno-regulation, as well as in
fibrosis and carcinogenesis (Roberts and Sporn (1990) see
above).

Activins and inhibins were originally identified as
factors which regulate secretion of follicle-stimulating
25 hormone secretion (Vale *et al* (1990) Peptide Growth Factors
and Their Receptors, Pt.2, Sporn and Roberts, eds. (Berlin:
Springer-Verlag) pp.211-248). Activins were also shown to
induce the differentiation of haematopoietic progenitor
cells (Murata *et al* (1988) Proc. Natl. Acad. Sci. USA 85,
30 2434 - 2438; Eto *et al* (1987) Biochem. Biophys. Res.
Commun. 142, 1095-1103) and induce mesoderm formation in
Xenopus embryos (Smith *et al* (1990) Nature 345, 729-731;
van den Eijnden-Van Raaij *et al* (1990) Nature 345, 732-
734).

35 BMPs or osteogenic proteins which induce the formation
of bone and cartilage when implanted subcutaneously (Wozney
et al (1988) Science 242, 1528-1534), facilitate neuronal

differentiation (Paralkar *et al* (1992) *J. Cell Biol.* **119**, 1721-1728) and induce monocyte chemotaxis (Cunningham *et al* (1992) *Proc. Natl. Acad. Sci. USA* **89**, 11740-11744). Müllerian-inhibiting substance induces regression of the 5 Müllerian duct in the male reproductive system (Cate *et al* (1986) *Cell* **45**, 685-698), and a glial cell line-derived neurotrophic factor enhances survival of midbrain dopaminergic neurons (Lin *et al* (1993) *Science* **260**, 1130-10 1132). The action of these growth factors is mediated through binding to specific cell surface receptors.

Within this family, TGF- β receptors have been most thoroughly characterized. By covalently cross-linking radio-labelled TGF- β to cell surface molecules followed by polyacrylamide gel electrophoresis of the affinity-labelled complexes, three distinct size classes of cell surface proteins (in most cases) have been identified, denoted receptor type I (53 kd), type II (75 kd), type III or betaglycan (a 300 kd proteoglycan with a 120 kd core protein) (for a review see Massague (1992) *Cell* **69** 1067-15 1070) and more recently endoglin (a homodimer of two 95 kd subunits) (Cheifetz *et al* (1992) *J. Biol. Chem.* **267** 19027-20 19030). Current evidence suggests that type I and type II receptors are directly involved in receptor signal transduction (Segarini *et al* (1989) *Mol. Endo.*, **3**, 261-272; 25 Laiho *et al* (1991) *J. Biol. Chem.* **266**, 9100-9112) and may form a heteromeric complex; the type II receptor is needed for the binding of TGF- β to the type I receptor and the type I receptor is needed for the signal transduction induced by the type II receptor (Wrana *et al* (1992) *Cell*, 30 **71**, 1003-1004). The type III receptor and endoglin may have more indirect roles, possibly by facilitating the binding of ligand to type II receptors (Wang *et al* (1991) *Cell*, **67** 797-805; López-Casillas *et al* (1993) *Cell*, **73** 1435-1444).

35 Binding analyses with activin A and BMP4 have led to the identification of two co-existing cross-linked affinity complexes of 50-60 kDa and 70-80 kDa on responsive cells

(Hino *et al* (1989) *J. Biol. Chem.* **264**, 10309 - 10314; Mathews and Vale (1991), *Cell* **68**, 775-785; Paralkar *et al* (1991) *Proc. Natl. Acad. Sci. USA* **87**, 8913-8917). By analogy with TGF- β receptors they are thought to be 5 signalling receptors and have been named type I and type II receptors.

Among the type II receptors for the TGF- β superfamily of proteins, the cDNA for the activin type II receptor (Act RII) was the first to be cloned (Mathews and Vale (1991) 10 *Cell* **65**, 973-982). The predicted structure of the receptor was shown to be a transmembrane protein with an intracellular serine/threonine kinase domain. The activin receptor is related to the *C. elegans* *daf-1* gene product, but the ligand is currently unknown (Georgi *et al* (1990) 15 *Cell* **61**, 635-645). Thereafter, another form of the activin type II receptor (activin type IIB receptor), of which there are different splicing variants (Mathews *et al* (1992), *Science* **225**, 1702-1705; Attisano *et al* (1992) *Cell* **68**, 97-108), and the TGF- β type II receptor (TBRII) (Lin *et* 20 *al* (1992) *Cell* **68**, 775-785) were cloned, both of which have putative serine/threonine kinase domains.

Summary of the Invention

The present invention involves the discovery of related novel peptides, including peptides having the 25 activity of those defined herein as SEQ ID Nos. 2, 4, 8, 10, 12, 14, 16 and 18. Their discovery is based on the realisation that receptor serine/threonine kinases form a new receptor family, which may include the type II receptors for other proteins in the TGF- β superfamily. To 30 ascertain whether there were other members of this family of receptors, a protocol was designed to clone ActRII/*daf* I related cDNAs. This approach made use of the polymerase chain reaction (PCR), using degenerate primers based upon the amino-acid sequence similarity between kinase domains 35 of the mouse activin type II receptor and *daf-1* gene products.

This strategy resulted in the isolation of a new family of receptor kinases called Activin receptor like kinases (ALK's) 1-6. These cDNAs showed an overall 33-39% sequence similarity with ActRII and TGF- β type II receptor 5 and 40-92% sequence similarity towards each other in the kinase domains.

Soluble receptors according to the invention comprise at least predominantly the extracellular domain. These can be selected from the information provided herein, prepared 10 in conventional manner, and used in any manner associated with the invention.

Antibodies to the peptides described herein may be raised in conventional manner. By selecting unique 15 sequences of the peptides, antibodies having desired specificity can be obtained.

The antibodies may be monoclonal, prepared in known manner. In particular, monoclonal antibodies to the extracellular domain are of potential value in therapy.

Products of the invention are useful in diagnostic 20 methods, e.g. to determine the presence in a sample for an analyte binding therewith, such as in an antagonist assay. Conventional techniques, e.g. an enzyme-linked immunosorbent assay, may be used.

Products of the invention having a specific receptor 25 activity can be used in therapy, e.g. to modulate conditions associated with activin or TGF- β activity. Such conditions include fibrosis, e.g. liver cirrhosis and pulmonary fibrosis, cancer, rheumatoid arthritis and glomeronephritis.

30 Brief Description of the Drawings

Figure 1 shows the alignment of the serine/threonine (S/T) kinase domains (I-VIII) of related receptors from transmembrane proteins, including embodiments of the present invention. The nomenclature of the subdomains is 35 accordingly to Hanks *et al* (1988).

Figures 2A to 2D shows the sequences and characteristics of the respective primers used in the

initial PCR reactions. The nucleic acid sequences are also given as SEQ ID Nos. 19 to 22.

Figure 3 is a comparison of the amino-acid sequences of human activin type II receptor (Act R-II), mouse activin type IIB receptor (Act R-IIB), human TGF- β type II receptor (T β R-II), human TGF- β type I receptor (ALK-5), human activin receptor type IA (ALK-2), and type IB (ALK-4), ALKs 1 & 3 and mouse ALK-6.

Figure 4 shows, schematically, the structures for Daf-1, Act R-II, Act R-IIB, T β R-II, T β R-I/ALK-5, ALK's -1, -2 (Act RIA), -3, -4 (Act RIB) & -6.

Figure 5 shows the sequence alignment of the cysteine-rich domains of the ALKs, T β R-II, Act R-II, Act R-IIB and daf-1 receptors.

Figure 6 is a comparison of kinase domains of serine/threonine kinases, showing the percentage amino-acid identity of the kinase domains.

Figure 7 shows the pairwise alignment relationship between the kinase domains of the receptor serine/threonine kinases. The dendrogram was generated using the Jotun-Hein alignment program (Hein (1990) Meth. Enzymol. 183, 626-645).

Brief Description of the Sequence Listings

Sequences 1 and 2 are the nucleotide and deduced amino-acid sequences of cDNA for hALK-1 (clone HP57).

Sequences 3 and 4 are the nucleotide and deduced amino-acid sequences of cDNA for hALK-2 (clone HP53).

Sequences 5 and 6 are the nucleotide and deduced amino-acid sequences of cDNA for hALK-3 (clone ONF5).

Sequences 7 and 8 the nucleotide and deduced amino-acid sequences of cDNA for hALK-4 (clone 11H8), complemented with PCR product encoding extracellular domain.

Sequences 9 and 10 are the nucleotide and deduced amino-acid sequences of cDNA for hALK-5 (clone EMLA).

Sequences 11 and 12 are the nucleotide and deduced amino-acid sequences of cDNA for mALK-1 (clone AM6).

Sequences 13 and 14 are the nucleotide and deduced amino-acid sequences of cDNA for mALK-3 (clones ME-7 and ME-D).

5 Sequences 15 and 16 are the nucleotide and deduced amino-acid sequences of cDNA for mALK-4 (clone 8a1).

Sequences 17 and 18 are the nucleotide and deduced amino-acid sequences of cDNA for mALK-6 (clone ME-6).

10 Sequence 19 (B1-S) is a sense primer, extracellular domain, cysteine-rich region, BamHI site at 5' end, 28-mer, 64-fold degeneracy.

Sequence 20 (B3-S) is a sense primer, kinase domain II, BamHI site at 5' end, 25-mer, 162-fold degeneracy.

15 Sequence 21 (B7-S) is a sense primer, kinase domain VIB, S/T kinase specific residues, BamHI site at 5' end, 24-mer, 288-fold degeneracy.

Sequence 22 (E8-AS) is an anti-sense primer, kinase domain, S/T kinase-specific residues EcoRI site at 5' end, 20-mer, 18-fold degeneracy.

Sequence 23 is an oligonucleotide probe.

20 Sequence 24 is a 5' primer.

Sequence 25 is a 3' primer.

Sequence 26 is a consensus sequence in Subdomain I.

Sequences 27 and 28 are novel sequence motifs in Subdomain VIB.

25 Sequence 29 is a novel sequence motif in Subdomain VIII.

Description of the Invention

As described in more detail below, nucleic acid sequences have been isolated, coding for a new sub-family 30 of serine/threonine receptor kinases. The term nucleic acid molecules as used herein refers to any sequence which codes for the murine, human or mammalian form, amino-acid sequences of which are presented herein. It is understood that the well known phenomenon of codon degeneracy provides 35 for a great deal of sequence variation and all such varieties are included within the scope of this invention.

The nucleic acid sequences described herein may be used to clone the respective genomic DNA sequences in order to study the genes' structure and regulation. The murine and human cDNA or genomic sequences can also be used to 5 isolate the homologous genes from other mammalian species. The mammalian DNA sequences can be used to study the receptors' functions in various in vitro and in vivo model systems.

As exemplified below for ALK-5 cDNA, it is also 10 recognised that, given the sequence information provided herein, the artisan could easily combine the molecules with a pertinent promoter in a vector, so as to produce a cloning vehicle for expression of the molecule. The promoter and coding molecule must be operably linked via 15 any of the well-recognized and easily-practised methodologies for so doing. The resulting vectors, as well as the isolated nucleic acid molecules themselves, may be used to transform prokaryotic cells (e.g. *E. coli*), or transfect eukaryotes such as yeast (*S. cerevisiae*), PAE, 20 COS or CHO cell lines. Other appropriate expression systems will also be apparent to the skilled artisan.

Several methods may be used to isolate the ligands for the ALKs. As shown for ALK-5 cDNA, cDNA clones encoding the active open reading frames can be subcloned into 25 expression vectors and transfected into eukaryotic cells, for example COS cells. The transfected cells which can express the receptor can be subjected to binding assays for radioactively-labelled members of the TGF- β superfamily (TGF- β , activins, inhibins, bone morphogenic proteins and müllerian-inhibiting substances), as it may be expected that the receptors will bind members of the TGF- β 30 superfamily. Various biochemical or cell-based assays can be designed to identify the ligands, in tissue extracts or conditioned media, for receptors in which a ligand is not known. Antibodies raised to the receptors may also be used 35 to identify the ligands, using the immunoprecipitation of the cross-linked complexes. Alternatively, purified

receptor could be used to isolate the ligands using an affinity-based approach. The determination of the expression patterns of the receptors may also aid in the isolation of the ligand. These studies may be carried out 5 using ALK DNA or RNA sequences as probes to perform in situ hybridisation studies.

The use of various model systems or structural studies should enable the rational development of specific agonists and antagonists useful in regulating receptor function. It 10 may be envisaged that these can be peptides, mutated ligands, antibodies or other molecules able to interact with the receptors.

The foregoing provides examples of the invention. Applicants intend to claim which includes, inter alia, 15 isolated nucleic acid molecules coding for activin receptor-like kinases (ALKs), as defined herein. These include such sequences isolated from mammalian species such as mouse, human, rat, rabbit and monkey.

The following description relates to specific 20 embodiments. It will be understood that the specification and examples are illustrative but not limitative of the present invention and that other embodiments within the spirit and scope of the invention will suggest themselves to those skilled in the art.

25 Preparation of mRNA and Construction of a cDNA Library

For construction of a cDNA library, poly (A)⁺ RNA was isolated from a human erythroleukemia cell line (HEL 92.1.7) obtained from the American Type Culture Collection (ATCC TIB 180). These cells were chosen as they have been 30 shown to respond to both activin and TGF- β . Moreover leukaemic cells have proved to be rich sources for the cloning of novel receptor tyrosine kinases (Partanen *et al* (1990) Proc. Natl. Acad. Sci. USA 87, 8913-8917 and (1992) Mol. Cell. Biol. 12, 1698-1707). (Total) RNA was prepared 35 by the guanidinium isothiocyanate method (Chirgwin *et al* (1979) Biochemistry 18, 5294-5299). mRNA was selected using the poly-A or poly AT tract mRNA isolation kit

(Promega, Madison, Wisconsin, U.S.A.) as described by the manufacturers, or purified through an oligo (dT)-cellulose column as described by Aviv and Leder (1972) Proc. Natl. Acad. Sci. USA 69, 1408-1412. The isolated mRNA was used 5 for the synthesis of random primed (Amersham) cDNA, that was used to make a λ gt10 library with 1×10^5 independent cDNA clones using the Riboclone cDNA synthesis system (Promega) and λ gt10 in vitro packaging kit (Amersham) according to the manufacturers' procedures. An amplified 10 oligo (dT) primed human placenta λ ZAPII cDNA library of 5×10^5 independent clones was used. Poly (A)⁺ RNA isolated from AG1518 human foreskin fibroblasts was used to prepare a primary random primed λ ZAPII cDNA library of 1.5×10^6 independent clones using the RiboClone cDNA synthesis 15 system and Gigapack Gold II packaging extract (Stratagene). In addition, a primary oligo (dT) primed human foreskin fibroblast λ gt10 cDNA library (Claesson-Welsh et al (1989) Proc. Natl. Acad. Sci. USA. 86 4917-4912) was prepared. An amplified oligo (dT) primed HEL cell λ gt11 cDNA library of 20 1.5×10^6 independent clones (Poncz et al (1987) Blood 69 219-223) was used. A twelve-day mouse embryo λ EXIox cDNA library was obtained from Novagen (Madison, Wisconsin, U.S.A.); a mouse placenta λ ZAPII cDNA library was also used.

25 Generation of cDNA Probes by PCR

For the generation of cDNA probes by PCR (Lee et al (1988) Science 239, 1288-1291) degenerate PCR primers were constructed based upon the amino-acid sequence similarity between the mouse activin type II receptor (Mathews and 30 Vale (1991) Cell 65, 973-982) and daf-1 (George et al (1990) Cell 61, 635-645) in the kinase domains II and VIII. Figure 1 shows the aligned serine/threonine kinase domains (I-VIII), of four related receptors of the TGF- β superfamily, i.e. hT β R-II, mActR-IIIB, mActR-II and the daf-35 1 gene product, using the nomenclature of the subdomains according to Hanks et al (1988) Science 241, 45-52.

Several considerations were applied in the design of the PCR primers. The sequences were taken from regions of homology between the activin type II receptor and the daf-1 gene product, with particular emphasis on residues that 5 confer serine/threonine specificity (see Table 2) and on residues that are shared by transmembrane kinase proteins and not by cytoplasmic kinases. The primers were designed so that each primer of a PCR set had an approximately similar GC composition, and so that self complementarity 10 and complementarity between the 3' ends of the primer sets were avoided. Degeneracy of the primers was kept as low as possible, in particular avoiding serine, leucine and arginine residues (6 possible codons), and human codon preference was applied. Degeneracy was particularly 15 avoided at the 3' end as, unlike the 5' end, where mismatches are tolerated, mismatches at the 3' end dramatically reduce the efficiency of PCR.

In order to facilitate directional subcloning, restriction enzyme sites were included at the 5' end of the 20 primers, with a GC clamp, which permits efficient restriction enzyme digestion. The primers utilised are shown in Figure 2. Oligonucleotides were synthesized using Gene assembler plus (Pharmacia - LKB) according to the manufacturers instructions.

25 The mRNA prepared from HEL cells as described above was reverse-transcribed into cDNA in the presence of 50 mM Tris-HCl, pH 8.3, 8 mM MgCl₂, 30 mM KCl, 10 mM dithiothreitol, 2mM nucleotide triphosphates, excess oligo (dT) primers and 34 units of AMV reverse transcriptase at 30 42°C for 2 hours in 40 µl of reaction volume. Amplification by PCR was carried out with a 7.5% aliquot (3 µl) of the reverse-transcribed mRNA, in the presence of 10 mM Tris-HCl, pH 8.3, 50 mM KCl, 1.5 M MgCl₂, 0.01% gelatin, 0.2 mM nucleotide triphosphates, 1 µM of both sense and 35 antisense primers and 2.5 units of Taq polymerase (Perkin Elmer Cetus) in 100 µl reaction volume. Amplifications were performed on a thermal cycler (Perkin Elmer Cetus)

using the following program: first 5 thermal cycles with denaturation for 1 minute at 94°C, annealing for 1 minute at 50°C, a 2 minute ramp to 55°C and elongation for 1 minute at 72°C, followed by 20 cycles of 1 minute at 94°C, 30 seconds at 55°C and 1 minute at 72°C. A second round of PCR was performed with 3 µl of the first reaction as a template. This involved 25 thermal cycles, each composed of 94°C (1 min), 55°C (0.5 min), 72°C (1 min).

General procedures such as purification of nucleic acids, restriction enzyme digestion, gel electrophoresis, transfer of nucleic acid to solid supports and subcloning were performed essentially according to established procedures as described by Sambrook *et al.* (1989), Molecular cloning: A Laboratory Manual, 2nd Ed. Cold Spring Harbor Laboratory (Cold Spring Harbor, New York, USA).

Samples of the PCR products were digested with BamHI and EcoRI and subsequently fractionated by low melting point agarose gel electrophoresis. Bands corresponding to the approximate expected sizes, (see Table 1: ≈460 bp for primer pair B3-S and E8-AS and ≈ 140 bp for primer pair B7-S and E8-AS) were excised from the gel and the DNA was purified. Subsequently, these fragments were ligated into pUC19 (Yanisch-Perron *et al* (1985) Gene 33, 103-119), which had been previously linearised with BamHI and EcoR1 and transformed into *E. coli* strain DH5 α using standard protocols (Sambrook *et al*, *supra*). Individual clones were sequenced using standard double-stranded sequencing techniques and the dideoxynucleotide chain termination method as described by Sanger *et al* (1977) Proc. Natl. Acad. Sci. USA 74, 5463-5467, and T7 DNA polymerase.

Employing Reverse Transcriptase PCR on HEL mRNA with the primer pair B3-S and E8-AS, three PCR products were obtained, termed 11.1, 11.2 and 11.3, that corresponded to novel genes. Using the primer pair B7-S and E8-AS, an additional novel PCR product was obtained termed 5.2.

TABLE 1

5	NAME OF PCR PRODUCT	PRIMERS	INSERT SIZE (bp)	SIZE OF DNA FRAGMENT IN mActRII/hT8RII CLONES (bp)	SEQUENCE IDENTITY WITH SEQUENCE mActRII/hT8RII (%)	SEQUENCE IDENTITY BETWEEN mActRII and T8R-II (%)
11.1	B3-S/E8-AS	460	460	460	46/40	42
11.2	B3-S/E8-AS	460	460	460	49/44	47
10	11.3	B3-S/E8-AS	460	460	44/36	48
11.29	B3-S/E8-AS	460	460	ND/100	ND	
9.2	B1-S/E8-AS	800	795	100/ND	ND	
5.2	B7-S/E8-AS	140	143	40/38	60	

15 Isolation of cDNA Clones

The PCR products obtained were used to screen various cDNA libraries described supra. Labelling of the inserts of PCR products was performed using random priming method (Feinberg and Vogelstein (1983) *Anal. Biochem.*, 132 6-13) using the Megaprime DNA labelling system (Amersham). The oligonucleotide derived from the sequence of the PCR product 5.2 was labelled by phosphorylation with T4 polynucleotide kinase following standard protocols (Sambrook *et al*, supra). Hybridization and purification of positive bacteriophages were performed using standard molecular biological techniques.

The double-stranded DNA clones were all sequenced using the dideoxynucleotide chain-termination method as described by Sanger *et al*, supra, using T7 DNA polymerase (Pharmacia - LKB) or Sequenase (U.S. Biochemical Corporation, Cleveland, Ohio, U.S.A.). Compressions of nucleotides were resolved using 7-deaza-GTP (U.S. Biochemical Corp.) DNA sequences were analyzed using the DNA STAR computer program (DNA STAR Ltd. U.K.). Analyses of the sequences obtained revealed the existence of six

distinct putative receptor serine/threonine kinases which have been named ALK 1-6.

To clone cDNA for ALK-1 the oligo (dT) primed human placenta cDNA library was screened with a radiolabelled insert derived from the PCR product 11.3; based upon their restriction enzyme digestion patterns, three different types of clones with approximate insert sizes of 1.7 kb, 2 kb & 3.5 kb were identified. The 2 kb clone, named HP57, was chosen as representative of this class and subjected to complete sequencing. Sequence analysis of ALK-1 revealed a sequence of 1984 nucleotides including a poly-A tail (SEQ ID No. 1). The longest open reading frame encodes a protein of 503 amino-acids, with high sequence similarity to receptor serine/threonine kinases (see below). The first methionine codon, the putative translation start site, is at nucleotide 283-285 and is preceded by an in-frame stop codon. This first ATG is in a more favourable context for translation initiation (Kozak (1987) Nucl. Acids Res., 15, 8125-8148) than the second and third in-frame ATG at nucleotides 316-318 and 325-327. The putative initiation codon is preceded by a 5' untranslated sequence of 282 nucleotides that is GC-rich (80% GC), which is not uncommon for growth factor receptors (Kozak (1991) J. Cell Biol., 115, 887-903). The 3' untranslated sequence comprises 193 nucleotides and ends with a poly-A tail. No bona fide poly-A addition signal is found, but there is a sequence (AATACA), 17-22 nucleotides upstream of the poly-A tail, which may serve as a poly-A addition signal.

ALK-2 cDNA was cloned by screening an amplified oligo (dT) primed human placenta cDNA library with a radiolabelled insert derived from the PCR product 11.2. Two clones, termed HP53 and HP64, with insert sizes of 2.7 kb and 2.4 kb respectively, were identified and their sequences were determined. No sequence difference in the overlapping clones was found, suggesting they are both derived from transcripts of the same gene.

Sequence analysis of cDNA clone HP53 (SEQ ID No. 3) revealed a sequence of 2719 nucleotides with a poly-A tail. The longest open reading frame encodes a protein of 509 amino-acids. The first ATG at nucleotides 104-106 agrees 5 favourably with Kozak's consensus sequence with an A at position 3. This ATG is preceded in-frame by a stop codon. There are four ATG codons in close proximity further downstream, which agree with the Kozak's consensus sequence (Kozak, *supra*), but according to Kozak's scanning model the 10 first ATG is predicted to be the translation start site. The 5' untranslated sequence is 103 nucleotides. The 3' untranslated sequence of 1089 nucleotides contains a polyadenylation signal located 9-14 nucleotides upstream from the poly-A tail. The cDNA clone HP64 lacks 498 15 nucleotides from the 5' end compared to HP53, but the sequence extended at the 3' end with 190 nucleotides and poly-A tail is absent. This suggests that different polyadenylation sites occur for ALK-2. In Northern blots, however, only one transcript was detected (see below).

20 The cDNA for human ALK-3 was cloned by initially screening an oligo (dT) primed human foreskin fibroblast cDNA library with an oligonucleotide (SEQ ID No. 23) derived from the PCR product 5.2. One positive cDNA clone with an insert size of 3 kb, termed ON11, was identified. 25 However, upon partial sequencing, it appeared that this clone was incomplete; it encodes only part of the kinase domain and lacks the extracellular domain. The most 5' sequence of ON11, a 540 nucleotide XbaI restriction fragment encoding a truncated kinase domain, was 30 subsequently used to probe a random primed fibroblast cDNA library from which one cDNA clone with an insert size of 3 kb, termed ONF5, was isolated (SEQ ID No. 5). Sequence analysis of ONF5 revealed a sequence of 2932 nucleotides without a poly-A tail, suggesting that this clone was 35 derived by internal priming. The longest open reading frame codes for a protein of 532 amino-acids. The first ATG codon which is compatible with Kozak's consensus

sequence (Kozak, supra), is at 310-312 nucleotides and is preceded by an in-frame stop codon. The 5' and 3' untranslated sequences are 309 and 1027 nucleotides long, respectively.

5 ALK-4 cDNA was identified by screening a human oligo (dT) primed human erythroleukemia cDNA library with the radiolabelled insert of the PCR product 11.1 as a probe. One cDNA clone, termed 11H8, was identified with an insert size of 2 kb (SEQ ID No. 7). An open reading frame was
10 found encoding a protein sequence of 383 amino-acids encoding a truncated extracellular domain with high similarity to receptor serine/threonine kinases. The 3' untranslated sequence is 818 nucleotides and does not contain a poly-A tail, suggesting that the cDNA was
15 internally primed. cDNA encoding the complete extracellular domain (nucleotides 1-366) was obtained from HEL cells by RT-PCR with 5' primer (SEQ ID No. 24) derived in part from sequence at translation start site of SKR-2 (a cDNA sequence deposited in GenBank data base, accession
20 number L10125, that is identical in part to ALK-4) and 3' primer (SEQ ID No. 25) derived from 11H8 cDNA clone.

ALK-5 was identified by screening the random primed HEL cell λgt 10 cDNA library with the PCR product 11.1 as a probe. This yielded one positive clone termed EMLA (insert size of 5.3 kb with 2 internal EcoRI sites). Nucleotide sequencing revealed an open reading frame of 1509 bp, coding for 503 amino-acids. The open reading frame was flanked by a 5' untranslated sequence of 76 bp, and a 3' untranslated sequence of 3.7 kb which was not
25 completely sequenced. The nucleotide and deduced amino-acid sequences of ALK-5 are shown in SEQ ID Nos. 9 and 10. In the 5' part of the open reading frame, only one ATG codon was found; this codon fulfills the rules of
30 translation initiation (Kozak, supra). An in-frame stop codon was found at nucleotides (-54)-(-52) in the 5' untranslated region. The predicted ATG start codon is followed by a stretch of hydrophobic amino-acid residues

which has characteristics of a cleavable signal sequence. Therefore, the first ATG codon is likely to be used as a translation initiation site. A preferred cleavage site for the signal peptidase, according to von Heijne (1986) *Nucl. Acid. Res.* **14**, 4683-4690, is located between amino-acid residues 24 and 25. The calculated molecular mass of the primary translated product of the ALK-5 without signal sequence is 53,646 Da.

Screening of the mouse embryo λ EX 1ox cDNA library using PCR, product 11.1 as a probe yielded 20 positive clones. DNAs from the positive clones obtained from this library were digested with EcoRI and HindIII, electrophoretically separated on a 1.3% agarose gel and transferred to nitrocellulose filters according to established procedures as described by Sambrook *et al.*, supra. The filters were then hybridized with specific probes for human ALK-1 (nucleotide 288-670), ALK-2 (nucleotide 1-581), ALK-3 (nucleotide 79-824) or ALK-4 (nucleotide 1178-1967). Such analyses revealed that a clone termed ME-7 hybridised with the human ALK-3 probe. However, nucleotide sequencing revealed that this clone was incomplete, and lacked the 5' part of the translated region. Screening the same cDNA library with a probe corresponding to the extracellular domain of human ALK-3 (nucleotides 79-824) revealed the clone ME-D. This clone was isolated and the sequence was analyzed. Although this clone was incomplete in the 3' end of the translated region, ME-7 and ME-D overlapped and together covered the complete sequence of mouse ALK-3. The predicted amino-acid sequence of mouse ALK-3 is very similar to the human sequence; only 8 amino-acid residues differ (98% identity; see SEQ ID No. 14) and the calculated molecular mass of the primary translated product without the putative signal sequence is 57,447 Da.

Of the clones obtained from the initial library screening with PCR product 11.1, four clones hybridized to the probe corresponding to the conserved kinase domain of

ALK-4 but not to probes from more divergent parts of ALK-1 to -4. Analysis of these clones revealed that they have an identical sequence which differs from those of ALK-1 to -5 and was termed ALK-6. The longest clone ME6 with a 2.0 kb 5 insert was completely sequenced yielding a 1952 bp fragment consisting of an open reading frame of 1506 bp (502 amino-acids), flanked by a 5' untranslated sequence of 186 bp, and a 3' untranslated sequence of 160 bp. The nucleotide and predicted amino-acid sequences of mouse ALK-6 are shown 10 in SEQ ID Nos. 17 and 18. No polyadenylation signal was found in the 3' untranslated region of ME6, indicating that the cDNA was internally primed in the 3' end. Only one ATG codon was found in the 5' part of the open reading frame, which fulfils the rules for translation initiation (Kozak, 15 supra), and was preceded by an in-frame stop codon at nucleotides 163-165. However, a typical hydrophobic leader sequence was not observed at the N terminus of the translated region. Since there is no ATG codon and putative hydrophobic leader sequence, this ATG codon is 20 likely to be used as a translation initiation site. The calculated molecular mass of the primary translated product with the putative signal sequence is 55,576 Da.

Mouse ALK-1 (clone AM6 with 1.9 kb insert) was obtained from the mouse placenta λ ZAPII cDNA library using 25 human ALK-1 cDNA as a probe (see SEQ ID No. 11). Mouse ALK-4 (clone 8a1 with 2.3kb insert) was also obtained from this library using human ALK-4 cDNA library as a probe (SEQ ID No. 15).

To summarise, clones HP22, HP57, ONF1, ONF3, ONF4 and 30 HP29 encode the same gene, ALK-1. Clone AM6 encodes mouse ALK-1. HP53, HP64 and HP84 encode the same gene, ALK-2. ONF5, ONF2 and ON11 encode the same gene ALK-3. ME-7 and ME-D encode the mouse counterpart of human ALK-3. 11H8 encodes a different gene ALK-4, whilst 8a1 encodes the 35 mouse equivalent. EMLA encodes ALK-5, and ME-6 encodes ALK-6.

The sequence alignment between the 6 ALK genes and TBR-II, mActR-II and ActR-IIB is shown in Figure 3. These molecules have a similar domain structure; an N-terminal predicted hydrophobic signal sequence (von Heijne (1986) 5 Nucl. Acids Res. 14: 4683-4690) is followed by a relatively small extracellular cysteine-rich ligand binding domain, a single hydrophobic transmembrane region (Kyte & Doolittle (1982) J. Mol. Biol. 157, 105-132) and a C-terminal intracellular portion, which consists almost entirely of a 10 kinase domain (Figures 3 and 4).

The extracellular domains of these receptors have cysteine-rich regions, but they show little sequence similarity; for example, less than 20% sequence identity is found between Daf-1, ActR-II, TBR-II and ALK-5. The ALKs 15 appear to form a subfamily as they show higher sequence similarities (15-47% identity) in their extracellular domains. The extracellular domains of ALK-5 and ALK-4 have about 29% sequence identity. In addition, ALK-3 and ALK-6 share a high degree of sequence similarity in their 20 extracellular domains (46% identity).

The positions of many of the cysteine residues in all receptors can be aligned, suggesting that the extracellular domains may adopt a similar structural configuration. See Figure 5 for ALKs-1,-2,-3 & -5. Each of the ALKs (except 25 ALK-6) has a potential N-linked glycosylation site, the position of which is conserved between ALK-1 and ALK-2, and between ALK-3, ALK-4 and ALK-5 (see Figure 4).

The sequence similarities in the kinase domains between daf-1, ActR-II, TBR-II and ALK-5 are approximately 30 40%, whereas the sequence similarity between the ALKs 1 to 6 is higher (between 59% and 90%; see Figure 6). Pairwise comparison using the Jutun-Hein sequence alignment program (Hein (1990) Meth. Enzymol., 183, 626-645), between all family members, identifies the ALKs as a separate subclass 35 among serine/threonine kinases (Figure 7).

The catalytic domains of kinases can be divided into 12 subdomains with stretches of conserved amino-acid

residues. The key motifs are found in serine/threonine kinase receptors suggesting that they are functional kinases. The consensus sequence for the binding of ATP (Gly-X-Gly-X-X-Gly in subdomain I followed by a Lys residue 5 further downstream in subdomain II) is found in all the ALKs.

The kinase domains of daf-1, ActR-II, and ALKs show approximately equal sequence similarity with tyrosine and serine/threonine protein kinases. However analysis of the 10 amino-acid sequences in subdomains VI and VIII, which are the most useful to distinguish a specificity for phosphorylation of tyrosine residues versus serine/threonine residues (Hanks et al (1988) Science **241** 42-52) indicates that these kinases are serine/threonine 15 kinases; refer to Table 2.

TABLE 2

KINASE	SUBDOMAINS	
	VIB	VIII
Serine/threonine kinase consensus	DLKPEN	G (T/S) XX (Y/F) X
5 Tyrosine kinase consensus	DLAARN	XP(I/V) (K/R) W (T/M)
Act R-II	DIKSKN	GTRRYM
Act R-IIB	DFKSKN	GTRRYM
TBR-II	DLKSSN	GTARYM
ALK-I	DFKSRN	GTKRYM
10 ALK -2, -3, -4, -5, & -6	DLKSKN	GTKRYM

The sequence motifs DLKSKN (Subdomain VIB) and GTKRYM (Subdomain VIII), that are found in most of the serine/threonine kinase receptors, agree well with the 15 consensus sequences for all protein serine/threonine kinase receptors in these regions. In addition, these receptors, except for ALK-1, do not have a tyrosine residue surrounded by acidic residues between subdomains VII and VIII, which is common for tyrosine kinases. A unique characteristic of 20 the members of the ALK serine/threonine kinase receptor family is the presence of two short inserts in the kinase

domain between subdomains VIA and VIB and between subdomains X and XI. In the intracellular domain, these regions, together with the juxtamembrane part and C-terminal tail, are the most divergent between family members (see Figures 3 and 4). Based on the sequence similarity with the type II receptors for TGF- β and activin, the C termini of the kinase domains of ALKs -1 to -6 are set at Ser-495, Ser-501, Ser-527, Gln-500, Gln-498 and Ser-497, respectively.

10 mRNA Expression

The distribution of ALK-1, -2, -3, -4 was determined by Northern blot analysis. A Northern blot filter with mRNAs from different human tissues was obtained from Clontech (Palo Alto, C.A.). The filters were hybridized 15 with 32 P-labelled probes at 42°C overnight in 50% formaldehyde, 5 x standard saline citrate (SSC; 1xSSC is 50mM sodium citrate, pH 7.0, 150 mM NaCl), 0.1% SDS, 50 mM sodium phosphate, 5 x Denhardt's solution and 0.1 mg/ml salmon sperm DNA. In order to minimize cross-hybridization, probes were used that did not encode part of 20 the kinase domains, but corresponded to the highly diverged sequences of either 5' untranslated and ligand-binding regions (probes for ALK-1, -2 and -3) or 3' untranslated sequences (probe for ALK-4). The probes were labelled by 25 random priming using the Multiprime (or Mega-prime) DNA labelling system and [α - 32 P] dCTP (Feinberg & Vogelstein (1983) Anal. Biochem. 132: 6-13). Unincorporated label was removed by Sephadex G-25 chromatography. Filters were washed at 65°C, twice for 30 minutes in 2.5 x SSC, 0.1% SDS 30 and twice for 30 minutes in 0.3 x SSC, 0.1% SDS before being exposed to X-ray film. Stripping of blots was performed by incubation at 90-100°C in water for 20 minutes.

The ALK-5 mRNA size and distribution were determined 35 by Northern blot analysis as above. An EcoR1 fragment of 980bp of the full length ALK-5 cDNA clone, corresponding to the C-terminal part of the kinase domain and 3'

untranslated region (nucleotides 1259-2232 in SEQ ID No. 9) was used as a probe. The filter was washed twice in 0.5 x SSC, 0.1% SDS at 55°C for 15 minutes.

Using the probe for ALK-1, two transcripts of 2.2 and 4.9 kb were detected. The ALK-1 expression level varied strongly between different tissues, high in placenta and lung, moderate in heart, muscle and kidney, and low (to not detectable) in brain, liver and pancreas. The relative ratios between the two transcripts were similar in most tissues; in kidney, however, there was relatively more of the 4.9 kb transcript. By reprobing the blot with a probe for ALK-2, one transcript of 4.0 kb was detected with a ubiquitous expression pattern. Expression was detected in every tissue investigated and was highest in placenta and skeletal muscle. Subsequently the blot was reprobed for ALK-3. One major transcript of 4.4 kb and a minor transcript of 7.9 kb were detected. Expression was high in skeletal muscle, in which also an additional minor transcript of 10 kb was observed. Moderate levels of ALK-3 mRNA were detected in heart, placenta, kidney and pancreas, and low (to not detectable) expression was found in brain, lung and liver. The relative ratios between the different transcripts were similar in the tested tissues, the 4.4 kb transcript being the predominant one, with the exception for brain where both transcripts were expressed at a similar level. Probing the blot with ALK-4 indicated the presence of a transcript with the estimated size of 5.2 kb and revealed an ubiquitous expression pattern. The results of Northern blot analysis using the probe for ALK-5 showed that a 5.5 kb transcript is expressed in all human tissues tested, being most abundant in placenta and least abundant in brain and heart.

The distribution of mRNA for mouse ALK-3 and -6 in various mouse tissues was also determined by Northern blot analysis. A multiple mouse tissue blot was obtained from Clontech, Palo Alto, California, U.S.A. The filter was hybridized as described above with probes for mouse ALK-3

and ALK-6. The EcoRI-PstI restriction fragment, corresponding to nucleotides 79-1100 of ALK-3, and the SacI-HpaI fragment, corresponding to nucleotides 57-720 of ALK-6, were used as probes. The filter was washed at 65°C 5 twice for 30 minutes in 2.5 x SSC, 0.1% SDS and twice for 30 minutes with 0.3 x SSC, 0.1% SDS and then subjected to autoradiography.

Using the probe for mouse ALK-3, a 1.1 kb transcript was found only in spleen. By reprobing the blot with the 10 ALK-6 specific probe, a transcript of 7.2 kb was found in brain and a weak signal was also seen in lung. No other signal was seen in the other tissues tested, i.e. heart, liver, skeletal muscle, kidney and testis.

All detected transcript sizes were different, and thus 15 no cross-reaction between mRNAs for the different ALKs was observed when the specific probes were used. This suggests that the multiple transcripts of ALK-1 and ALK-3 are coded from the same gene. The mechanism for generation of the different transcripts is unknown at present; they may be 20 formed by alternative mRNA splicing, differential polyadenylation, use of different promoters, or by a combination of these events. Differences in mRNA splicing in the regions coding for the extracellular domains may 25 lead to the synthesis of receptors with different affinities for ligands, as was shown for mActR-IIB (Attisano *et al* (1992) *Cell* 68, 97-108) or to the production of soluble binding protein.

The above experiments describe the isolation of 30 nucleic acid sequences coding for new family of human receptor kinases. The cDNA for ALK-5 was then used to determine the encoded protein size and binding properties.
Properties of the ALKs cDNA Encoded Proteins

To study the properties of the proteins encoded by the 35 different ALK cDNAs, the cDNA for each ALK was subcloned into a eukaryotic expression vector and transfected into various cell types and then subjected to immunoprecipitation using a rabbit antiserum raised against

a synthetic peptide corresponding to part of the intracellular juxtamembrane region. This region is divergent in sequence between the various serine/threonine kinase receptors. The following amino-acid residues were 5 used:

ALK-1	145-166
ALK-2	151-172
ALK-3	181-202
ALK-4	153-171
10 ALK-5	158-179
ALK-6	151-168

The rabbit antiserum against ALK-5 was designated VPN.

The peptides were synthesized with an Applied Biosystems 430A Peptide Synthesizer using t-butoxycarbonyl 15 chemistry and purified by reversed-phase high performance liquid chromatography. The peptides were coupled to keyhole limpet haemocyanin (Calbiochem-Behring) using glutaraldehyde, as described by Guillick *et al* (1985) EMBO J. 4, 2869-2877. The coupled peptides were mixed with 20 Freunds adjuvant and used to immunize rabbits.

Transient transfection of the ALK-5 cDNA

COS-1 cells (American Type Culture Collection) and the R mutant of Mv1Lu cells (for references, see below) were cultured in Dulbecco's modified Eagle's medium containing 25 10% fetal bovine serum (FBS) and 100 units/ml penicillin and 50 µg/ml streptomycin in 5% CO₂ atmosphere at 37°C. The ALK-5 cDNA (nucleotides (-76) - 2232), which includes the complete coding region, was cloned in the pSV7d vector (Truett *et al*, (1985) DNA 4, 333-349), and used for 30 transfection. Transfection into COS-1 cells was performed by the calcium phosphate precipitation method (Wigler *et al* (1979) Cell 16, 777-785). Briefly, cells were seeded into 6-well cell culture plates at a density of 5x10⁵ cells/well, and transfected the following day with 10 µg of 35 recombinant plasmid. After overnight incubation, cells were washed three times with a buffer containing 25 mM Tris-HCl, pH 7.4, 138 mM NaCl, 5 mM KCl, 0.7 mM CaCl₂, 0.5

5 mM MgCl₂ and 0.6 mM Na₂HPO₄, and then incubated with Dulbecco's modified Eagle's medium containing FBS and antibiotics. Two days after transfection, the cells were metabolically labelled by incubating the cells for 6 hours
5 in methionine and cysteine-free MCDB 104 medium with 150 µCi/ml of [³⁵S]-methionine and [³⁵S]-cysteine (in vivo labelling mix; Amersham). After labelling, the cells were washed with 150 mM NaCl, 25 mM Tris-HCl, pH 7.4, and then solubilized with a buffer containing 20mM Tris-HCl, pH 7.4,
10 150 mM NaCl, 10 mM EDTA, 1% Triton X-100, 1% deoxycholate, 1.5% Trasylol (Bayer) and 1 mM phenylmethylsulfonylfluoride (PMSF; Sigma). After 15 minutes on ice, the cell lysates were pelleted by centrifugation, and the supernatants were then incubated with 7 µl of preimmune serum for 1.5 hours
15 at 4°C. Samples were then given 50 µl of protein A-Sepharose (Pharmacia-LKB) slurry (50% packed beads in 150 mM NaCl, 20 mM Tris-HCl, pH 7.4, 0.2% Triton X100) and incubated for 45 minutes at 4°C. The beads were spun down by centrifugation, and the supernatants (1 ml) were then
20 incubated with either 7 µl of preimmune serum or the VPN antiserum for 1.5 hours at 4°C. For blocking, 10 µg of peptide was added together with the antiserum. Immune complexes were then given 50 µl of protein A-Sepharose (Pharmacia - LKB) slurry (50% packed beads in 150 mM NaCl,
25 20mM Tris-HCl, pH 7.4, 0.2% Triton X-100) and incubated for 45 minutes at 4°C. The beads were spun down and washed four times with a washing buffer (20 mM Tris-HCl, pH 7.4, 500 mM NaCl, 1% Triton X-100, 1% deoxycholate and 0.2% SDS), followed by one wash in distilled water. The immune
30 complexes were eluted by boiling for 5 minutes in the SDS-sample buffer (100 mM Tris-HCl, pH 8.8, 0.01% bromophenol blue, 36% glycerol, 4% SDS) in the presence of 10 mM DTT, and analyzed by SDS-gel electrophoresis using 7-15% polyacrylamide gels (Blobel and Dobberstein, (1975) J.Cell Biol. 67, 835-851). Gels were fixed, incubated with Amplify (Amersham) for 20 minutes, and subjected to fluorography. A component of 53Da was seen. This
35

component was not seen when preimmune serum was used, or when 10 µg blocking peptide was added together with the antiserum. Moreover, it was not detectable in samples derived from untransfected COS-1 cells using either 5 preimmune serum or the antiserum.

Digestion with Endoglycosidase F

Samples immunoprecipitated with the VPN antisera obtained as described above were incubated with 0.5 U of endoglycosidase F (Boehringer Mannheim Biochemica) in a 10 buffer containing 100 mM sodium phosphate, pH 6.1, 50 mM EDTA, 1% Triton X-100, 0.1% SDS and 1% β -mercaptoethanol at 37°C for 24 hours. Samples were eluted by boiling for 5 minutes in the SDS-sample buffer, and analyzed by SDS-polyacrylamide gel electrophoresis as described above. 15 Hydrolysis of N-linked carbohydrates by endoglycosidase F shifted the 53 kDa band to 51 kDa. The extracellular domain of ALK-5 contains one potential acceptor site for N-glycosylation and the size of the deglycosylated protein is close to the predicted size of the core protein.

20 Establishment of PAE Cell Lines Expressing ALK-5

In order to investigate whether the ALK-5 cDNA encodes a receptor for TGF- β , porcine aortic endothelial (PAE) cells were transfected with an expression vector containing the ALK-5 cDNA, and analyzed for the binding of 125 I-TGF- β 1.

25 PAE cells were cultured in Ham's F-12 medium supplemented with 10% FBS and antibiotics (Miyazono *et al.*, (1988) *J. Biol. Chem.* **263**, 6407-6415). The ALK-5 cDNA was cloned into the cytomegalovirus (CMV)-based expression vector pcDNA I/NEO (Invitrogen), and transfected into PAE 30 cells by electroporation. After 48 hours, selection was initiated by adding Geneticin (G418 sulphate; Gibco - BRL) to the culture medium at a final concentration of 0.5 mg/ml (Westerman *et al.*, (1990) *Proc. Natl. Acad. Sci. USA* **87**, 128-132). Several clones were obtained, and after analysis 35 by immunoprecipitation using the VPN antiserum, one clone denoted PAE/TBR-1 was chosen and further analyzed.

Iodination of TGF- β 1, Binding and Affinity Crosslinking

Recombinant human TGF- β 1 was iodinated using the chloramine T method according to Frolik *et al.*, (1984) *J. Biol. Chem.* **259**, 10995-11000. Cross-linking experiments were performed as previously described (Ichijo *et al.*, (1990) *Exp. Cell Res.* **187**, 263-269). Briefly, cells in 6-well plates were washed with binding buffer (phosphate-buffered saline containing 0.9 mM CaCl₂, 0.49 mM MgCl₂, and 1 mg/ml bovine serum albumin (BSA)), and incubated on ice in the same buffer with ¹²⁵I-TGF- β 1 in the presence or absence of excess unlabelled TGF- β 1 for 3 hours. Cells were washed and cross-linking was done in the binding buffer without BSA together with 0.28 mM disuccinimidyl suberate (DSS; Pierce Chemical Co.) for 15 minutes on ice. The cells were harvested by the addition of 1 ml of detachment buffer (10 mM Tris-HCl, pH 7.4, 1 mM EDTA, 10% glycerol, 0.3 mM PMSF). The cells were pelleted by centrifugation, then resuspended in 50 μ l of solubilization buffer (125 mM NaCl, 10 mM Tris-HCl, pH 7.4, 1 mM EDTA, 1% Triton X-100, 0.3 mM PMSF, 1% Trasylol) and incubated for 40 minutes on ice. Cells were centrifuged again and supernatants were subjected to analysis by SDS-gel electrophoresis using 4-15% polyacrylamide gels, followed by autoradiography. ¹²⁵I-TGF- β 1 formed a 70 kDa cross-linked complex in the transfected PAE cells (PAE/T β R-I cells). The size of this complex was very similar to that of the TGF- β type I receptor complex observed at lower amounts in the untransfected cells. A concomitant increase of 94 kDa TGF- β type II receptor complex could also be observed in the PAE/T β R-I cells. Components of 150-190 kDa, which may represent crosslinked complexes between the type I and type II receptors, were also observed in the PAE/T β R-I cells.

In order to determine whether the cross-linked 70 kDa complex contained the protein encoded by the ALK-5 cDNA, the affinity cross-linking was followed by immunoprecipitation using the VPN antiserum. For this,

cells in 25 cm² flasks were used. The supernatants obtained after cross-linking were incubated with 7 μ l of preimmune serum or VPN antiserum in the presence or absence of 10 μ g of peptide for 1.5h at 4°C. Immune complexes were 5 then added to 50 μ l of protein A-Sepharose slurry and incubated for 45 minutes at 4°C. The protein A-Sepharose beads were washed four times with the washing buffer, once with distilled water, and the samples were analyzed by SDS-gel electrophoresis using 4-15% polyacrylamide gradient 10 gels and autoradiography. A 70 kDa cross-linked complex was precipitated by the VPN antiserum in PAE/TBR-I cells, and a weaker band of the same size was also seen in the untransfected cells, indicating that the untransfected PAE cells contained a low amount of endogenous ALK-5. The 70 15 kDa complex was not observed when preimmune serum was used, or when immune serum was blocked by 10 μ g of peptide. Moreover, a coprecipitated 94 kDa component could also be observed in the PAE/TBR-I cells. The latter component is likely to represent a TGF- β type II receptor complex, since 20 an antiserum, termed DRL, which was raised against a synthetic peptide from the C-terminal part of the TGF- β type II receptor, precipitated a 94 kDa TGF- β type II receptor complex, as well as a 70 kDa type I receptor complex from PAE/TBR-I cells.

25 The carbohydrate contents of ALK-5 and the TGF- β type II receptor were characterized by deglycosylation using endoglycosidase F as described above and analyzed by SDS-polyacrylamide gel electrophoresis and autoradiography. The ALK-5 cross-linked complex shifted from 70 kDa to 66 30 kDa, whereas that of the type II receptor shifted from 94 kDa to 82 kDa. The observed larger shift of the type II receptor band compared with that of the ALK-5 band is consistent with the deglycosylation data of the type I and type II receptors on rat liver cells reported previously 35 (Cheifetz *et al* (1988) *J. Biol. Chem.* 263, 16984-16991), and fits well with the fact that the porcine TGF- β type II receptor has two N-glycosylation sites (Lin *et al* (1992)

Cell 68, 775-785), whereas ALK-5 has only one (see SEQ ID No. 9).

Binding of TGF- β 1 to the type I receptor is known to be abolished by transient treatment of the cells with 5 dithiothreitol (DTT) (Cheifetz and Massague (1991) J. Biol. Chem. 266, 20767-20772; Wrana *et al* (1992) Cell 71, 1003-1014). When analyzed by affinity cross-linking, binding of 125 I-TGF- β 1 to ALK-5, but not to the type II receptor, was completely abolished by DTT treatment of PAE/TBR-1 cells. 10 Affinity cross-linking followed by immunoprecipitation by the VPN antiserum showed that neither the ALK-5 nor the type II receptor complexes was precipitated after DTT treatment, indicating that the VPN antiserum reacts only with ALK-5. The data show that the VPN antiserum 15 recognizes a TGF- β type I receptor, and that the type I and type II receptors form a heteromeric complex.

125 I-TGF- β 1 Binding & Affinity Crosslinking of Transfected COS Cells

Transient expression plasmids of ALKs -1 to -6 and 20 TBR-II were generated by subcloning into the pSV7d expression vector or into the pcDNA I expression vector (Invitrogen). Transient transfection of COS-1 cells and iodination of TGF- β 1 were carried out as described above. Crosslinking and immunoprecipitation were performed as 25 described for PAE cells above.

Transfection of cDNAs for ALKs into COS-1 cells did not show any appreciable binding of 125 I-TGF β 1, consistent with the observation that type I receptors do not bind TGF- β in the absence of type II receptors. When the TBR-II 30 cDNA was co-transfected with cDNAs for the different ALKs, type I receptor-like complexes were seen, at different levels, in each case. COS-1 cells transfected with TBR-II and ALK cDNAs were analyzed by affinity crosslinking followed by immunoprecipitation using the DRL antisera or 35 specific antisera against ALKs. Each one of the ALKs bound 125 I-TGF- β 1 and was coimmunoprecipitated with the TBR-II complex using the DRL antiserum. Comparison of the

efficiency of the different ALKs to form heteromeric complexes with TBR-II, revealed that ALK-5 formed such complexes more efficiently than the other ALKs. The size of the crosslinked complex was larger for ALK-3 than for 5 other ALKs, consistent with its slightly larger size.

Expression of the ALK Protein in Different Cell Types

Two different approaches were used to elucidate which ALK's are physiological type I receptors for TGF- β .

Firstly, several cell lines were tested for the expression of the ALK proteins by cross-linking followed by immunoprecipitation using the specific antiseras against ALKs and the TGF- β type II receptor. The mink lung epithelial cell line, Mv1Lu, is widely used to provide target cells for TGF- β action and is well characterized 10 regarding TGF- β receptors (Laiho *et al* (1990) *J. Biol. Chem.* 265, 18518-18524; Laiho *et al* (1991) *J. Biol. Chem.* 266, 9108-9112). Only the VPN antiserum efficiently precipitated both type I and type II TGF- β receptors in the wild type Mv1Lu cells. The DRL antiserum also precipitated 15 components with the same size as those precipitated by the VPN antiserum. A mutant cell line (R mutant) which lacks the TGF- β type I receptor and does not respond to TGF- β (Laiho *et al*, *supra*) was also investigated by cross-linking followed by immunoprecipitation. Consistent with the 20 results obtained by Laiho *et al* (1990), *supra* the type III and type II TGF- β receptor complexes, but not the type I receptor complex, were observed by affinity crosslinking. Crosslinking followed by immunoprecipatition using the DRL 25 antiserum revealed only the type II receptor complex, whereas neither the type I nor type II receptor complexes was seen using the VPN antiserum. When the cells were metabolically labelled and subjected to immunoprecipitation 30 using the VPN antiserum, the 53 kDa ALK-5 protein was precipitated in both the wild-type and R mutant Mv1Lu cells. These results suggest that the type I receptor 35 expressed in the R mutant is ALK-5, which has lost the affinity for binding to TGF- β after mutation.

The type I and type II TGF- β receptor complexes could be precipitated by the VPN and DRL antisera in other cell lines, including human foreskin fibroblasts (AG1518), human lung adenocarcinoma cells (A549), and human oral squamous cell carcinoma cells (HSC-2). Affinity cross-linking studies revealed multiple TGF- β type I receptor-like complexes of 70-77 kDa in these cells. These components were less efficiently competed by excess unlabelled TGF- β 1 in HSC-2 cells. Moreover, the type II receptor complex was low or not detectable in A549 and HSC-2 cells. Cross-linking followed by immunoprecipitation revealed that the VPN antiserum precipitated only the 70 kDa complex among the 70-77 kDa components. The DRL antiserum precipitated the 94 kDa type II receptor complex as well as the 70 kDa type I receptor complex in these cells, but not the putative type I receptor complexes of slightly larger sizes. These results suggest that multiple type I TGF- β receptors may exist and that the 70 kDa complex containing ALK-5 forms a heteromeric complex with the TGF- β type II receptor cloned by Lin *et al* (1992) *Cell* 68, 775-785, more efficiently than the other species. In rat pheochromocytoma cells (PC12) which have been reported to have no TGF- β receptor complexes by affinity cross-linking (Massagué *et al* (1990) *Ann. N.Y. Acad. Sci.* 593, 59-72), neither VPN nor DRL antisera precipitated the TGF- β receptor complexes. The antisera against ALKs -1 to -4 and ALK6 did not efficiently immunoprecipitate the crosslinked receptor complexes in porcine aortic endothelial (PAE) cells or human foreskin fibroblasts.

Next, it was investigated whether ALKs could restore responsiveness to TGF- β in the R mutant of Mv1Lu cells, which lack the ligand-binding ability of the TGF- β type I receptor but have intact type II receptor. Wild-type Mv1Lu cells and mutant cells were transfected with ALK cDNA and were then assayed for the production of plasminogen activator inhibitor-1 (PAI-1) which is produced as a result of TGF- β receptor activation as described previously by

Laiho *et al* (1991) Mol. Cell Biol. 11, 972-978. Briefly, cells were added with or without 10 ng/ml of TGF- β 1 for 2 hours in serum-free MCDB 104 without methionine. Thereafter, cultures were labelled with [35 S] methionine (40 5 μ Ci/ml) for 2 hours. The cells were removed by washing on ice once in PBS, twice in 10 mM Tris-HCl (pH 8.0), 0.5% sodium deoxycholate, 1 mM PMSF, twice in 2 mM Tris-HCl (pH 8.0), and once in PBS. Extracellular matrix proteins were extracted by scraping cells into the SDS-sample buffer 10 containing DTT, and analyzed by SDS-gel electrophoresis followed by fluorography using Amplify. PAI-1 can be identified as a characteristic 45kDa band (Laiho *et al* (1991) Mol. Cell Biol. 11, 972-978). Wild-type Mv1Lu cells responded to TGF- β and produced PAI-1, whereas the R mutant 15 clone did not, even after stimulation by TGF- β 1. Transient transfection of the ALK-5 cDNA into the R mutant clone led to the production of PAI-1 in response to the stimulation by TGF- β 1, indicating that the ALK-5 cDNA encodes a functional TGF- β type I receptor. In contrast, the R 20 mutant cells that were transfected with other ALKs did not produce PAI-1 upon the addition of TGF- β 1.

Using similar approaches as those described above for the identification of TGF- β -binding ALKs, the ability of ALKs to bind activin in the presence of ActRII was 25 examined. COS-1 cells were co-transfected as described above. Recombinant human activin A was iodinated using the chloramine T method (Mathews and Vale (1991) Cell 65, 973-982). Transfected COS-1 cells were analysed for binding and crosslinking of 125 I-activin A in the presence or 30 absence of excess unlabelled activin A. The crosslinked complexes were subjected to immunoprecipitation using DRL antisera or specific ALK antisera.

All ALKs appear to bind activin A in the presence of Act R-II. This is more clearly demonstrated by affinity 35 cross-linking followed by immunoprecipitation. ALK-2 and ALK-4 bound 125 I-activin A and were coimmunoprecipitated

with ActR-II. Other ALKs also bind ¹²⁵I-activin A but with a lower efficiency compared to ALK-2 and ALK-4.

In order to investigate whether ALKs are physiological activin type I receptors, activin responsive cells were 5 examined for the expression of endogenous activin type I receptors. Mv1Lu cells, as well as the R mutant, express both type I and type II receptors for activin, and the R mutant cells produce PAI-1 upon the addition of activin A. Mv1Lu cells were labeled with ¹²⁵I-activin A, cross-linked 10 and immunoprecipitated by the antisera against ActR-II or ALKs as described above.

The type I and type II receptor complexes in Mv1Lu cells were immunoprecipitated only by the antisera against ALK-2, ALK-4 and ActR-II. Similar results were obtained 15 using the R mutant cells. PAE cells do not bind activin because of the lack of type II receptors for activin, and so cells were transfected with a chimeric receptor, to enable them to bind activin, as described herein. A plasmid (chim A) containing the extracellular domain and C- 20 terminal tail of Act R-II (amino-acids -19 to 116 and 465 to 494, respectively (Mathews and Vale (1991) Cell, 65, 973-982)) and the kinase domain of TBR-II (amino-acids 160-543) (Lin *et al* (1992) Cell, 68, 775-785) was constructed and transfected into pcDNA/neo (Invitrogen). PAE cells 25 were stably transfected with the chim A plasmid by electroporation, and cells expressing the chim A protein were established as described previously. PAE/Chim A cells were then subjected to ¹²⁵I-activin A labelling crosslinking and immunoprecipitation as described above.

Similar to Mv1Lu cells, activin type I receptor complexes in PAE/Chim A cells were immunoprecipitated by the ALK-2 and ALK-4 antisera. These results show that both ALK-2 and ALK-4 serve as high affinity type I receptors for activin A in these cells.

35 ALK-1, ALK-3 and ALK-6 bind TGF- β 1 and activin A in the presence of their respective type II receptors, but the

functional consequences of the binding of the ligands remains to be elucidated.

The invention has been described by way of example only, without restriction of its scope. The invention is 5 defined by the subject matter herein, including the claims that follow the immediately following full Sequence Listings.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

- (A) NAME: Ludwig Institute for Cancer Research
- (B) STREET: St. Mary's Hospital Medical School, Norfolk Place
- (C) CITY: Paddington, London
- (E) COUNTRY: United Kingdom
- (F) POSTAL CODE (ZIP): W2 1PG

(ii) TITLE OF INVENTION: PROTEINS HAVING SERINE/THREONINE KINASE DOMAINS, CORRESPONDING NUCLEIC ACID MOLECULES, AND THEIR USE

(iii) NUMBER OF SEQUENCES: 29

(iv) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Floppy disk
- (B) COMPUTER: IBM PC compatible
- (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1984 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(vii) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 283..1791

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

AGGAAACGGT TTATTAGGAG GGAGTGGTGG AGCTGGGCCA GGCAGGAAGA CGCTGGAATA	60
AGAAACATTT TTGCTCCAGC CCCCATCCCA GTCCCGGGAG GCTGCCGCC CAGCTGCGCC	120
GAGCGAGCCC CTCCCCGGCT CCAGCCCCGT CCGGGGCCGC GCGGGACCCC AGCCCGCCGT	180
CCAGCGCTGG CGGTGCAACT GCGGCCGCC GGTGGAGGGG AGGTGGCCCC GGTCGCCGA	240

AGGCTAGCGC CCCGCCACCC GCAGAGCGGG CCCAGAGGGA CC ATG ACC TTG GGC Met Thr Leu Gly	294
1	
TCC CCC AGG AAA GGC CTT CTG ATG CTG CTG ATG GCC TTG GTG ACC CAG Ser Pro Arg Lys Gly Leu Leu Met Leu Leu Met Ala Leu Val Thr Gln 5 10 15 20	342
GGA GAC CCT GTG AAG CCG TCT CCG GGC CCG CTG GTG ACC TGC ACG TGT Gly Asp Pro Val Lys Pro Ser Arg Gly Pro Leu Val Thr Cys Thr Cys 25 30 35	390
GAG AGC CCA CAT TGC AAG GGG CCT ACC TGC CCG GGG CCC TCG TGC ACA Glu Ser Pro His Cys Lys Gly Pro Thr Cys Arg Gly Ala Trp Cys Thr 40 45 50	438
GTA GTG CTG GTG CCG GAG GGG AGG CAC CCC CAG GAA CAT CGG GGC Val Val Leu Val Arg Glu Glu Gly Arg His Pro Gln Glu His Arg Gly 55 60 65	486
TGC CGG AAC TTG CAC ACC GAG CTC TGC AGG GGG CCC CCC ACC GAG TTC Cys Gly Asn Leu His Arg Glu Leu Cys Arg Gly Arg Pro Thr Glu Phe 70 75 80	534
GTC AAC CAC TAC TGC TGC GAC AGC CAC CTC TGC AAC CAC AAC GTG TCC Val Asn His Tyr Cys Cys Asp Ser His Leu Cys Asn His Asn Val Ser 85 90 95 100	582
CTG GTG CTG GAG GCC ACC CAA CCT CCT TCG GAG CAG CCG GGA ACA GAT Leu Val Leu Glu Ala Thr Gln Pro Pro Ser Glu Gln Pro Gly Thr Asp 105 110 115	630
GCC CAG CTG GCC CTG ATC CTG GGC CCC GTG CTG GCC TTG CTG GCC CTG Gly Gln Leu Ala Leu Ile Leu Gly Pro Val Leu Ala Leu Leu Ala Leu 120 125 130	678
GTG GCC CTG GGT GTC CTG CCC CTG TGG CAT GTC CCA CGG AGG CAG GAG Val Ala Leu Gly Val Leu Gly Leu Trp His Val Arg Arg Arg Gln Glu 135 140 145	726
AAG CAG CGT GGC CTG CAC ACC GAG CTG GGA GAG TCC AGT CTC ATC CTG Lys Gln Arg Gly Leu His Ser Glu Leu Gly Glu Ser Ser Leu Ile Leu 150 155 160	774
AAA GCA TCT GAG CAG GGC GAC ACG ATG TTG GGG GAC CTC CTG GAC AGT Lys Ala Ser Glu Gln Gly Asp Thr Met Leu Gly Asp Leu Leu Asp Ser 165 170 175 180	822
GAC TGC ACC ACA GGG AGT GGC TCA GGG CTC CCC TTC CTG GTG CAG AGG Asp Cys Thr Thr Gly Ser Gly Ser Gly Leu Pro Phe Leu Val Gln Arg 185 190 195	870
ACA CTG GCA CGG CAG GTT GCC TTG GTG GAG TGT GTG GGA AAA GGC CGC Thr Val Ala Arg Gln Val Ala Leu Val Glu Cys Val Gly Lys Gly Arg 200 205 210	918
TAT GGC GAA GTG TGG CGG GGC TTG TGG CAC GGT GAG AGT GTG GCC GTC Tyr Gly Glu Val Trp Arg Gly Leu Trp His Gly Glu Ser Val Ala Val 215 220 225	966

AAG ATC TTC TCC TCG AGG GAT GAA CAG TCC TGG TTC CGG CAG ACT GAG Lys Ile Phe Ser Ser Arg Asp Glu Gln Ser Trp Phe Arg Glu Thr Glu 230 235 240	1014
ATC TAT AAC ACA GTA TTG CTC AGA CAC GAC AAC ATC CTA GGC TTC ATC Ile Tyr Asn Thr Val Leu Leu Arg His Asp Asn Ile Leu Gly Phe Ile 245 250 255 260	1062
GCC TCA GAC ATG ACC TCC CGC AAC TCG AGC ACG CAG CTG TGG CTC ATC Ala Ser Asp Met Thr Ser Arg Asn Ser Ser Thr Gln Leu Trp Leu Ile 265 270 275	1110
ACG CAC TAC CAC GAG CAC GGC TCC CTC TAC GAC TTT CTG CAG AGA CAG Thr His Tyr His Glu His Gly Ser Leu Tyr Asp Phe Leu Gln Arg Gln 280 285 290	1158
ACG CTG GAG CCC CAT CTG GCT CTG AGG CTA GCT GTG TCC GCG GCA TGC Thr Leu Glu Pro His Leu Ala Leu Arg Leu Ala Val Ser Ala Ala Cys 295 300 305	1206
GGC CTG GCG CAC CTG CAC GTG GAG ATC TTC GGT ACA CAG GGC AAA CCA Gly Leu Ala His Leu His Val Glu Ile Phe Gly Thr Gln Gly Lys Pro 310 315 320	1254
GCC ATT GCC CAC CGC GAC TTC AAG AGC CGC AAT GTG CTG GTC AAG AGC Ala Ile Ala His Arg Asp Phe Lys Ser Arg Asn Val Leu Val Lys Ser 325 330 335 340	1302
AAC CTG CAG TGT TGC ATC GCC GAC CTG GGC CTG GCT GTG ATG CAC TCA Asn Leu Gln Cys Cys Ile Ala Asp Leu Gly Leu Ala Val Met His Ser 345 350 355	1350
CAG GGC ACC GAT TAC CTG GAC ATC GGC AAC AAC CCG AGA GTG GGC ACC Gln Gly Ser Asp Tyr Leu Asp Ile Gly Asn Asn Pro Arg Val Gly Thr 360 365 370	1398
AAG CGG TAC ATG GCA CCC GAG GTG CTG GAC GAG CAG ATC CGC ACG GAC Lys Arg Tyr Met Ala Pro Glu Val Leu Asp Glu Gln Ile Arg Thr Asp 375 380 385	1446
TGC TTT GAG TCC TAC AAG TGG ACT GAC ATC TGG GCC TTT CGC CTG GTG Cys Phe Glu Ser Tyr Lys Trp Thr Asp Ile Trp Ala Phe Gly Leu Val 390 395 400	1494
CTG TGG GAG ATT GCC CGC CGG ACC ATC GTG AAT GGC ATC GTG GAG GAC Leu Trp Glu Ile Ala Arg Arg Thr Ile Val Asn Gly Ile Val Glu Asp 405 410 415 420	1542
TAT AGA CCA CCC TTC TAT GAT GTG GTG CCC AAT GAC CCC ACC TTT GAG Tyr Arg Pro Pro Phe Tyr Asp Val Val Pro Asn Asp Pro Ser Phe Glu 425 430 435	1590
GAC ATG AAG AAG GTG GTG TGT GTG GAT CAG CAG ACC CCC ACC ATC CCT Asp Met Lys Lys Val Val Cys Val Asp Gln Gln Thr Pro Thr Ile Pro 440 445 450	1638
AAC CGG CTG GCT GCA GAC CCG GTC CTC TCA GGC CTA GCT CAG ATG ATG Asn Arg Leu Ala Ala Asp Pro Val Leu Ser Gly Leu Ala Gln Met Met 455 460 465	1686

CGG GAG TGC TGG TAC CCA AAC CCC TCT GCC CGA CTC ACC GCG CTC CGG	1734
Arg Glu Cys Trp Tyr Pro Asn Pro Ser Ala Arg Leu Thr Ala Leu Arg	
470 475 480	
ATC AAG AAG ACA CTA CAA AAA ATT AGC AAC AGT CCA GAG AAG CCT AAA	1782
Ile Lys Lys Thr Leu Gln Lys Ile Ser Asn Ser Pro Glu Lys Pro Lys	
485 490 495 500	
GTG ATT CAA TAGCCCCAGGA GCACCTGATT CCTTTCTGCC TGCAGGGGGC	1831
Val Ile Gln	
TGGGGGGGGTG GGGGGCACTG GATGGTGCCC TATCTGGTA GAGGTAGTGT GAGTGTGGTG	1891
TGTGCTGGGG ATGGGCAGCT GCGCCTGCCT GCTCGGCCCC CAGCCCACCC AGCCAAAAAT	1951
ACAGCTGGGC TGAAACCTGA AAAAAAAAAA AAA	1984

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 503 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Met Thr Leu Gly Ser Pro Arg Lys Gly Leu Leu Met Leu Leu Met Ala	
1 5 10 15	
Leu Val Thr Gln Gly Asp Pro Val Lys Pro Ser Arg Gly Pro Leu Val	
20 25 30	
Thr Cys Thr Cys Glu Ser Pro His Cys Lys Gly Pro Thr Cys Arg Gly	
35 40 45	
Ala Trp Cys Thr Val Val Leu Val Arg Glu Glu Gly Arg His Pro Gln	
50 55 60	
Glu His Arg Gly Cys Gly Asn Leu His Arg Glu Leu Cys Arg Gly Arg	
65 70 75 80	
Pro Thr Glu Phe Val Asn His Tyr Cys Cys Asp Ser His Leu Cys Asn	
85 90 95	
His Asn Val Ser Leu Val Leu Glu Ala Thr Gln Pro Pro Ser Glu Gln	
100 105 110	
Pro Gly Thr Asp Gly Gln Leu Ala Leu Ile Leu Gly Pro Val Leu Ala	
115 120 125	
Leu Leu Ala Leu Val Ala Leu Gly Val Leu Gly Leu Trp His Val Arg	
130 135 140	
Arg Arg Gln Glu Lys Gln Arg Gly Leu His Ser Glu Leu Gly Glu Ser	
145 150 155 160	

Ser Leu Ile Leu Lys Ala Ser Glu Gln Gly Asp Thr Met Leu Gly Asp
 165 170 175
 Leu Leu Asp Ser Asp Cys Thr Thr Gly Ser Gly Ser Gly Leu Pro Phe
 180 185 190
 Leu Val Gln Arg Thr Val Ala Arg Gln Val Ala Leu Val Glu Cys Val
 195 200 205
 Gly Lys Gly Arg Tyr Gly Glu Val Trp Arg Gly Leu Trp His Gly Glu
 210 215 220
 Ser Val Ala Val Lys Ile Phe Ser Ser Arg Asp Glu Gln Ser Trp Phe
 225 230 235 240
 Arg Glu Thr Glu Ile Tyr Asn Thr Val Leu Leu Arg His Asp Asn Ile
 245 250 255
 Leu Gly Phe Ile Ala Ser Asp Met Thr Ser Arg Asn Ser Ser Thr Gln
 260 265 270
 Leu Trp Leu Ile Thr His Tyr His Glu His Gly Ser Leu Tyr Asp Phe
 275 280 285
 Leu Gln-Arg-Gln Thr-Leu Glu Pro His Leu Ala Leu Arg Leu Ala Val
 290 295 300
 Ser Ala Ala Cys Gly Leu Ala His Leu His Val Glu Ile Phe Gly Thr
 305 310 315 320
 Gln Gly Lys Pro Ala Ile Ala His Arg Asp Phe Lys Ser Arg Asn Val
 325 330 335
 Leu Val Lys Ser Asn Leu Gln Cys Cys Ile Ala Asp Leu Gly Leu Ala
 340 345 350
 Val Met His Ser Gln Gly Ser Asp Tyr Leu Asp Ile Gly Asn Asn Pro
 355 360 365
 Arg Val Gly Thr Lys Arg Tyr Met Ala Pro Glu Val Leu Asp Glu Gln
 370 375 380
 Ile Arg Thr Asp Cys Phe Glu Ser Tyr Lys Trp Thr Asp Ile Trp Ala
 385 390 395 400
 Phe Gly Leu Val Leu Trp Glu Ile Ala Arg Arg Thr Ile Val Asn Gly
 405 410 415
 Ile Val Glu Asp Tyr Arg Pro Pro Phe Tyr Asp Val Val Pro Asn Asp
 420 425 430
 Pro Ser Phe Glu Asp Met Lys Lys Val Val Cys Val Asp Gln Gln Thr
 435 440 445
 Pro Thr Ile Pro Asn Arg Leu Ala Ala Asp Pro Val Leu Ser Gly Leu
 450 455 460
 Ala Gln Met Met Arg Glu Cys Trp Tyr Pro Asn Pro Ser Ala Arg Leu
 465 470 475 480

Thr Ala Leu Arg Ile Lys Lys Thr Leu Gln Lys Ile Ser Asn Ser Pro
 485 490 495

Glu Lys Pro Lys Val Ile Gln
 500

(2) INFORMATION FOR SEQ ID NO: 3:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2724 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (v) FRAGMENT TYPE: internal
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: Homo sapiens
- (ix) FEATURE:
 - (A) NAME/KEY: CDS
 - (B) LOCATION: 104..1630

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

CTCCGAGTAC CCCAGTGACC AGAGTGAGAG AAGCTCTGAA CGAGGGCACCG CGGCTTGAAG	60
GACTGTGGGC AGATGTGACC AAGAGCCTGC ATTAAGTTGT ACA ATG GTA GAT GGA	115
Met Val Asp Gly	
1	
G TG ATG ATT CTT CCT GTG CTT ATC ATG ATT GCT CTC CCC TCC CCT AGT	163
Val Met Ile Leu Pro Val Leu Ile Met Ile Ala Leu Pro Ser Pro Ser	
5 10 15 20	
ATG GAA GAT GAG AAG CCC AAG GTC AAC CCC AAA CTC TAC ATG TGT GTG	211
Met Glu Asp Glu Lys Pro Lys Val Asn Pro Lys Leu Tyr Met Cys Val	
25 30 35	
TGT GAA GGT CTC TCC TGC GGT AAT GAG GAC CAC TGT GAA GGC CAG CAG	259
Cys Glu Gly Leu Ser Cys Gly Asn Glu Asp His Cys Glu Gly Gln Gln	
40 45 50	
TGC TTT TCC TCA CTG AGC ATC AAC GAT GGC TTC CAC GTC TAC CAG AAA	307
Cys Phe Ser Ser Leu Ser Ile Asn Asp Gly Phe His Val Tyr Gln Lys	
55 60 65	
GGC TGC TTC CAG GTT TAT GAG CAG GGA AAG ATG ACC TGT AAG ACC CCG	355
Gly Cys Phe Gln Val Tyr Glu Gln Gly Lys Met Thr Cys Lys Thr Pro	
70 75 80	

CCG TCC CCT GGC CAA GCT GTG GAG TGC TGC CAA GGG GAC TGG TGT AAC Pro Ser Pro Gly Gln Ala Val Glu Cys Cys Gln Gly Asp Trp Cys Asn 85 90 95 100	403
AGG AAC ATC ACG GCC CAG CTG CCC ACT AAA GGA AAA TCC TTC CCT GGA Arg Asn Ile Thr Ala Gln Leu Pro Thr Lys Gly Lys Ser Phe Pro Gly 105 110 115	451
ACA CAG AAT TTC CAC TTG GAG GTT GGC CTC ATT ATT CTC TCT GTA GTG Thr Gln Asn Phe His Leu Glu Val Gly Leu Ile Ile Leu Ser Val Val 120 125 130	499
TTC GCA GTA TGT CTT TTA GCC TGC CTG CTG GGA GTT GCT CTC CGA AAA Phe Ala Val Cys Leu Leu Ala Cys Leu Leu Gly Val Ala Leu Arg Lys 135 140 145	547
TTT AAA AGG CGC AAC CAA GAA CGC CTC AAT CCC CGA GAC GTG GAG TAT Phe Lys Arg Arg Asn Gln Glu Arg Leu Asn Pro Arg Asp Val Glu Tyr 150 155 160	595
GGC ACT ATC GAA GGG CTC ATC ACC ACC AAT GTT GGA GAC AGC ACT TTA Gly Thr Ile Glu Gly Leu Ile Thr Thr Asn Val Gly Asp Ser Thr Leu 165 170 175 180	643
GCA GAT TTA TTG GAT CAT TCG TGT ACA TCA CGA AGT GGC TCT CGT CTT Ala Asp Leu Leu Asp His Ser Cys Thr Ser Gly Ser Gly Ser Gly Leu 185 190 195	691
CCT TTT CTG GTA CAA AGA ACA GTG GCT CGC CAG ATT ACA CTG TTG GAG Pro Phe Leu Val Gln Arg Thr Val Ala Arg Gln Ile Thr Leu Leu Glu 200 205 210	739
TGT GTC GGG AAA GGC AGG TAT GGT GAG GTG TGG AGG GGC AGC TGG CAA Cys Val Gly Lys Gly Arg Tyr Gly Glu Val Trp Arg Gly Ser Trp Gln 215 220 225	787
GGG GAA AAT GTT GCC GTG AAG ATC TTC TCC TCC CGT GAT GAG AAG TCA Gly Glu Asn Val Ala Val Lys Ile Phe Ser Ser Arg Asp Glu Lys Ser 230 235 240	835
TGG TTC AGG GAA ACG GAA TTG TAC AAC ACT GTG ATG CTG AGG CAT GAA Trp Phe Arg Glu Thr Glu Leu Tyr Asn Thr Val Met Leu Arg His Glu 245 250 255 260	883
AAT ATC TTA GGT TTC ATT GCT TCA GAC ATG ACA TCA AGA CAC TCC AGT Asn Ile Leu Gly Phe Ile Ala Ser Asp Met Thr Ser Arg His Ser Ser 265 270 275	931
ACC CAG CTG TGG TTA ATT ACA CAT TAT CAT GAA ATG GGA TCG TTG TAC Thr Gln Leu Trp Leu Ile Thr His Tyr His Glu Met Gly Ser Leu Tyr 280 285 290	979
GAC TAT CTT CAG CTT ACT ACT CTG GAT ACA GTT AGC TGC CTT CGA ATA Asp Tyr Leu Gln Leu Thr Thr Leu Asp Thr Val Ser Cys Leu Arg Ile 295 300 305	1027
GTG CTG TCC ATA GCT ACT GGT CTT GCA CAT TTG CAC ATA GAG ATA TTT Val Leu Ser Ile Ala Ser Gly Leu Ala His Leu His Ile Glu Ile Phe 310 315 320	1075

GGG ACC CAA GGG AAA CCA GCC ATT GCC CAT CGA GAT TTA AAG AGC AAA Gly Thr Gln Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys Ser Lys 325 330 335 340	1123
AAT ATT CTG CTT AAG AAG AAT GGA CAG TGT TGC ATA GCA GAT TTG GGC Asn Ile Leu Val Lys Lys Asn Gly Gln Cys Cys Ile Ala Asp Leu Gly 345 350 355	1171
CTG GCA GTC ATG CAT TCC CAG AGC ACC AAT CAG CTT GAT GTG GGG AAC Leu Ala Val Met His Ser Gln Ser Thr Asn Gln Leu Asp Val Gly Asn 360 365 370	1219
AAT CCC CGT GTG GGC ACC AAG CGC TAC ATG GCC CCC GAA GTT CTA GAT Asn Pro Arg Val Gly Thr Lys Arg Tyr Met Ala Pro Glu Val Leu Asp 375 380 385	1267
GAA ACC ATC CAG GTG GAT TGT TTC GAT TCT TAT AAA AGG GTC GAT ATT Glu Thr Ile Gln Val Asp Cys Phe Asp Ser Tyr Lys Arg Val Asp Ile 390 395 400	1315
TGG GCC TTT GGA CTT GTT TTG TGG GAA GTG GCC AGG CGG ATG GTG AGC Trp Ala Phe Gly Leu Val Leu Trp Glu Val Ala Arg Arg Met Val Ser 405 410 415 420	1363
AAT GGT ATA GTG GAG GAT TAC AAG CCA CCG TTC TAC GAT GTG GTT CCC Asn Gly Ile Val Glu Asp Tyr Lys Pro Pro Phe Tyr Asp Val Val Pro 425 430 435	1411
AAT GAC CCA AGT TTT GAA GAT ATG AGG AAG GTA GTC TGT GTG GAT CAA Asn Asp Pro Ser Phe Glu Asp Met Arg Lys Val Val Cys Val Asp Gln 440 445 450	1459
CAA AGG CCA AAC ATA CCC AAC AGA TGG TTC TCA GAC CCG ACA TTA ACC Gln Arg Pro Asn Ile Pro Asn Arg Trp Phe Ser Asp Pro Thr Leu Thr 455 460 465	1507
TCT CTG GCC AAG CTA ATG AAA GAA TGC TGG TAT CAA AAT CCA TCC GCA Ser Leu Ala Lys Leu Met Lys Glu Cys Trp Tyr Gln Asn Pro Ser Ala 470 475 480	1555
AGA CTC ACA GCA CTG CGT ATC AAA AAG ACT TTG ACC AAA ATT GAT AAT Arg Leu Thr Ala Leu Arg Ile Lys Lys Thr Leu Thr Lys Ile Asp Asn 485 490 495 500	1603
TCC CTC GAC AAA TTG AAA ACT GAC TGT TGACATTTTC ATAGTGTCAA Ser Leu Asp Lys Leu Lys Thr Asp Cys 505	1650
GAAGGAAGAT TTGACGTTGT TGTCATTGTC CAGCTGGAC CTAATGCTGG CCTGACTGGT TGTCAGAATG GAATCCATCT GTCTCCCTCC CCAAATGGCT GCTTTGACAA GGCAGACGTC	1710
GTACCCAGCC ATGTGTTGGG GAGACATCAA AACCAACCTA ACCTCGCTCG ATGACTGTGA	1770
ACTGGCATT TCACGAACTG TTCACACTGC AGAGACTAAT GTTGGACAGA CACTGTTGCA	1830
AAGGTAGGGA CTGGAGGAAC ACAGAGAAAT CCTAAAAGAG ATCTGGCAT TAAGTCAGTG	1890
GCTTTGCATA GCTTTCACAA GTCTCCTAGA CACTCCCCAC GGGAAACTCA AGGAGGTGGT	1950
	2010

GAATTTTAA TCAGCAATAT TGCCTGTGCT TCTCTTCTTT ATTGCACTAG GAATTCTTGT	2070
CATTCCTTAC TTGCACTGTT ACTCTTAATT TAAAGACCC AACTGCCAA AATGTTGGCT	2130
GCGTACTCCA CTGGTCTGTC TTTGGATAAT AGGAATTCAA TTTGGCAAAA CAAATGTAA	2190
TGTCAGACTT TGCTGCATT TACACATGTG CTGATGTTA CAATGATGCC GAACATTAGG	2250
AATTGTTAT ACACAACTTT GCAAATTATT TATTACTTGT GCACTTAGTA GTTTTACAA	2310
AACTGCTTG TGCAATATGTT AAAGCTTATT TTTATGTGGT CTTATGATTT TATTACAGAA	2370
ATGTTTTAA CACTATACTC TAAAATGGAC ATTTCTTTT ATTATCAGTT AAAATCACAT	2430
TTTAAGTGCT TCACTTTGT ATGTGTGTAG ACTGTAACCTT TTTTCAGTT CATATGCAGA	2490
ACGTATTTAG CCATTACCCA CGTGACACCA CCGAATATAT TATCGATTTA GAAGCAAAGA	2550
TTTCAGTAGA ATTTTAGTCC TGAACGCTAC GGGGAAAATG CATTTCCTTC AGAATTATCC	2610
ATTACGTGCA TTTAAACTCT GCCAGAAAAA AATAACTATT TTGTTTAAT CTACTTTTG	2670
TATTTAGTAG TTATTTGTAT AAATTAATA AACTGTTTC AAGTCAAAAA AAAA	2724

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 509 amino acids
- (B) TYPE: amino acid
- (C) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Met Val Asp Gly Val Met Ile Leu Pro Val Leu Ile Met Ile Ala Leu	
1 5 10 15	
Pro Ser Pro Ser Met Glu Asp Glu Lys Pro Lys Val Asn Pro Lys Leu	
20 25 30	
Tyr Met Cys Val Cys Glu Gly Leu Ser Cys Gly Asn Glu Asp His Cys	
35 40 45	
Glu Gly Gln Gln Cys Phe Ser Ser Leu Ser Ile Asn Asp Gly Phe His	
50 55 60	
Val Tyr Gln Lys Gly Cys Phe Gln Val Tyr Glu Gln Gly Lys Met Thr	
65 70 75 80	
Cys Lys Thr Pro Pro Ser Pro Gly Gln Ala Val Glu Cys Cys Gln Gly	
85 90 95	
Asp Trp Cys Asn Arg Asn Ile Thr Ala Gln Leu Pro Thr Lys Gly Lys	
100 105 110	
Ser Phe Pro Gly Thr Gln Asn Phe His Leu Glu Val Gly Leu Ile Ile	
115 120 125	

Leu Ser Val Val Phe Ala Val Cys Leu Leu Ala Cys Leu Leu Gly Val
 130 135 140
 Ala Leu Arg Lys Phe Lys Arg Arg Asn Gln Glu Arg Leu Asn Pro Arg
 145 150 155 160
 Asp Val Glu Tyr Gly Thr Ile Glu Gly Leu Ile Thr Thr Asn Val Gly
 165 170 175
 Asp Ser Thr Leu Ala Asp Leu Leu Asp His Ser Cys Thr Ser Gly Ser
 180 185 190
 Gly Ser Gly Leu Pro Phe Leu Val Gln Arg Thr Val Ala Arg Gln Ile
 195 200 205
 Thr Leu Leu Glu Cys Val Gly Lys Gly Arg Tyr Gly Glu Val Trp Arg
 210 215 220
 Gly Ser Trp Gln Gly Glu Asn Val Ala Val Lys Ile Phe Ser Ser Arg
 225 230 235 240
 Asp Glu Lys Ser Trp Phe Arg Glu Thr Glu Leu Tyr Asn Thr Val Met
 245 250 255
 Leu Arg His Glu Asn Ile Leu Gly Phe Ile Ala Ser Asp Met Thr Ser
 260 265 270
 Arg His Ser Ser Thr Gln Leu Trp Leu Ile Thr His Tyr His Glu Met
 275 280 285
 Gly Ser Leu Tyr Asp Tyr Leu Gln Leu Thr Thr Leu Asp Thr Val Ser
 290 295 300
 Cys Leu Arg Ile Val Leu Ser Ile Ala Ser Gly Leu Ala His Leu His
 305 310 315 320
 Ile Glu Ile Phe Gly Thr Gln Gly Lys Pro Ala Ile Ala His Arg Asp
 325 330 335
 Leu Lys Ser Lys Asn Ile Leu Val Lys Lys Asn Gly Gln Cys Cys Ile
 340 345 350
 Ala Asp Leu Gly Leu Ala Val Met His Ser Gln Ser Thr Asn Gln Leu
 355 360 365
 Asp Val Gly Asn Asn Pro Arg Val Gly Thr Lys Arg Tyr Met Ala Pro
 370 375 380
 Glu Val Leu Asp Glu Thr Ile Gln Val Asp Cys Phe Asp Ser Tyr Lys
 385 390 395 400
 Arg Val Asp Ile Trp Ala Phe Gly Leu Val Leu Trp Glu Val Ala Arg
 405 410 415
 Arg Met Val Ser Asn Gly Ile Val Glu Asp Tyr Lys Pro Pro Phe Tyr
 420 425 430
 Asp Val Val Pro Asn Asp Pro Ser Phe Glu Asp Met Arg Lys Val Val
 435 440 445

Cys Val Asp Gin Gln Arg Pro Asn Ile Pro Asn Arg Trp Phe Ser Asp
 450 455 460
 Pro Thr Leu Thr Ser Leu Ala Lys Leu Met Lys Glu Cys Trp Tyr Gln
 465 470 475 480
 Asn Pro Ser Ala Arg Leu Thr Ala Leu Arg Ile Lys Lys Thr Leu Thr
 485 490 495
 Lys Ile Asp Asn Ser Leu Asp Lys Leu Lys Thr Asp Cys
 500 505

(2) INFORMATION FOR SEQ ID NO: 5:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2932 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (v) FRAGMENT TYPE: internal
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: Homo sapiens
- (ix) FEATURE:
 - (A) NAME/KEY: CDS
 - (B) LOCATION: 310..1905

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

GCTCCGGGCC GAGGGCTGGA GGATGCGTTC CCTGGGTCC GGACTTATGA AAATATGCAT	60
CAGTTTAATA CTGTCTTGGA ATTCAATGAGA TCGAACATA GGTCAAAGCT GTTGGAGAA	120
AATCAGAACT ACAGTTTAT CTAGCCACAT CTTGGAGGAG TCGTAAGAAA GCAGTGGGAG	180
TTGAAGTCAT TGTCAAGTGC TTGCGATCTT TTACAAGAAA ATCTCACTGA ATGATAGTCA	240
TTTAAATTGG TGAAGTAGCA AGACCAATTAA TAAACGTGA CAGTACACAG GAAACATTAC	300
AATTGAACA ATG ACT CAG CTA TAC ATT TAC ATC AGA TTA TTG GGA GCC Met Thr Gln Leu Tyr Ile Tyr Ile Arg Leu Leu Gly Ala	348
1 5 10	
TAT TTG TTC ATC ATT TCT CGT GTT CAA GGA CAG AAT CTG GAT AGT ATG Tyr Leu Phe Ile Ile Ser Arg Val Gln Gln Asn Leu Asp Ser Met	396
15 20 25	

CTT CAT GGC ACT GGG ATG AAA TCA GAC TCC GAC CAG AAA AAG TCA GAA Leu His Gly Thr Gly Met Lys Ser Asp Ser Asp Gln Lys Lys Ser Glu 30 35 40 45	444
AAT GGA GTA ACC TTA GCA CCA GAG GAT ACC TTG CCT TTT TTA AAG TGC Asn Gly Val Thr Leu Ala Pro Glu Asp Thr Leu Pro Phe Leu Lys Cys 50 55 60	492
TAT TGC TCA GGG CAC TGT CCA GAT GAT GCT ATT AAT AAC ACA TGC ATA Tyr Cys Ser Gly His Cys Pro Asp Asp Ala Ile Asn Asn Thr Cys Ile 65 70 75	540
ACT AAT GGA CAT TGC TTT GCC ATC ATA GAA GAA GAT GAC CAG GGA GAA Thr Asn Gly His Cys Phe Ala Ile Ile Glu Glu Asp Asp Gln Gly Glu 80 85 90	588
ACC ACA TTA GCT TCA GGG TGT ATG AAA TAT GAA GGA TCT GAT TTT CAG Thr Thr Leu Ala Ser Gly Cys Met Lys Tyr Glu Gly Ser Asp Phe Gln 95 100 105	636
TGC AAA GAT TCT CCA AAA GCC CAG CTA CGC CCG ACA ATA GAA TGT TGT Cys Lys Asp Ser Pro Lys Ala Gln Leu Arg Arg Thr Ile Glu Cys Cys 110 115 120 125	684
CGG ACC AAT TTA TGT AAC CAG TAT TTG CAA CCC ACA CTG CCC CCT GTT Arg Thr Asn Leu Cys Asn Gln Tyr Leu Gln Pro Thr Leu Pro Pro Val 130 135 140	732
GTC ATA GGT CCG TTT TTT GAT GGC AGC ATT CGA TGG CTG GTT TTG CTC Val Ile Gly Pro Phe Asp Gly Ser Ile Arg Trp Leu Val Leu Leu 145 150 155	780
ATT TCT ATG GCT GTC ATA ATT GCT ATG ATC ATC TTC TCC AGC TGC Ile Ser Met Ala Val Cys Ile Ile Ala Met Ile Ile Phe Ser Ser Cys 160 165 170	828
TTT TGT TAC AAA CAT TAT TGC AAG AGC ATC TCA AGC AGA CGT CGT TAC Phe Cys Tyr Lys His Tyr Cys Lys Ser Ile Ser Ser Arg Arg Arg Tyr 175 180 185	876
AAT CGT GAT TTG GAA CAG GAT GAA GCA TTT ATT CCA GTT GGA GAA TCA Asn Arg Asp Leu Glu Gln Asp Glu Ala Phe Ile Pro Val Gly Glu Ser 190 195 200 205	924
CTA AAA GAC CTT ATT GAC CAG TCA CAA AGT TCT GGT AGT GGG TCT GGA Leu Lys Asp Leu Ile Asp Gln Ser Gln Ser Ser Gly Ser Gly Ser Gly 210 215 220	972
CTA CCT TTA TTG GTT CAG CGA ACT ATT GCC AAA CAG ATT CAG ATG GTC Leu Pro Leu Leu Val Gln Arg Thr Ile Ala Lys Gln Ile Gln Met Val 225 230 235	1020
CGG CAA GTT GGT AAA GGC CGA TAT GGA GAA GTA TGG ATG GGC AAA TGG Arg Gln Val Gly Lys Gly Arg Tyr Gly Glu Val Trp Met Gly Lys Trp 240 245 250	1068
CGT GGC GAA AAA GTG GCG GTG AAA GTA TTC TTT ACC ACT GAA GAA GCC Arg Gly Glu Lys Val Ala Val Lys Val Phe Phe Thr Thr Glu Glu Ala 255 260 265	1116

AGC TGG TTT CGA GAA ACA GAA ATC TAC CAA ACT GTG CTA ATG CGC CAT Ser Trp Phe Arg Glu Thr Glu Ile Tyr Glu Val Leu Met Arg His 270 275 280 285	1164
GAA AAC ATA CTT GGT TTC ATA GCG GCA GAC ATT AAA GGT ACA GGT TCC Glu Asn Ile Leu Gly Phe Ile Ala Ala Asp Ile Lys Gly Thr Gly Ser 290 295 300	1212
TGG ACT CAG CTC TAT TTG ATT ACT GAT TAC CAT GAA AAT GGA TCT CTC Trp Thr Gln Leu Tyr Leu Ile Thr Asp Tyr His Glu Asn Gly Ser Leu 305 310 315	1260
TAT GAC TTC CTG AAA TGT GCT ACA CTG GAC ACC AGA GCC CTG CTT AAA Tyr Asp Phe Leu Lys Cys Ala Thr Leu Asp Thr Arg Ala Leu Leu Lys 320 325 330	1308
TTG GCT TAT TCA GCT GCC TGT GGT CTG TGC CAC CTG CAC ACA GAA ATT Leu Ala Tyr Ser Ala Ala Cys Gly Leu Cys His Leu His Thr Glu Ile 335 340 345	1356
TAT GGC ACC CAA CGA AAG CCC GCA ATT CCT CAT CGA GAC CTA AAG AGC Tyr Gly Thr Gln Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys Ser 350 355 360 365	1404
AAA AAC ATC CTC ATC AAG AAA AAT GGG AGT TGC TGC ATT GCT GAC CTG Lys Asn Ile Leu Ile Lys Asn Gly Ser Cys Cys Ile Ala Asp Leu 370 375 380	1452
GGC CTT GCT GTT AAA TTC AAC AGT GAC ACA AAT GAA GTT GAT GTG CCC Gly Leu Ala Val Lys Phe Asn Ser Asp Thr Asn Glu Val Asp Val Pro 385 390 395	1500
TTG AAT ACC AGG GTG GGC ACC AAA CGC TAC ATG GCT CCC GAA GTG CTG Leu Asn Thr Arg Val Gly Thr Lys Arg Tyr Met Ala Pro Glu Val Leu 400 405 410	1548
GAC GAA AGC CTG AAC AAA AAC CAC TTC CAG CCC TAC ATC ATG GCT GAC Asp Glu Ser Leu Asn Lys Asn His Phe Gln Pro Tyr Ile Met Ala Asp 415 420 425	1596
ATC TAC AGC TTC GGC CTA ATC ATT TCG GAG ATG GCT CGT CGT TGT ATC Ile Tyr Ser Phe Gly Leu Ile Trp Glu Met Ala Arg Arg Cys Ile 430 435 440 445	1644
ACA GGA CGG ATC GTG GAA GAA TAC CAA TTG CCA TAT TAC AAC ATG GTA Thr Gly Ile Val Glu Glu Tyr Gln Leu Pro Tyr Tyr Asn Met Val 450 455 460	1692
CCG AGT GAT CCG TCA TAC GAA GAT ATG CGT GAG GTT GTG TGT GTC AAA Pro Ser Asp Pro Ser Tyr Glu Asp Met Arg Glu Val Val Cys Val Lys 465 470 475	1740
CGT TTG CGG CCA ATT GTG TCT AAT CGG TGG AAC AGT GAT GAA TGT CTA Arg Leu Arg Pro Ile Val Ser Asn Arg Trp Asn Ser Asp Glu Cys Leu 480 485 490	1788
CGA GCA GTT TTG AAG CTA ATG TCA GAA TGC TGG GCC CAC AAT CCA GCC Arg Ala Val Leu Lys Leu Met Ser Glu Cys Trp Ala His Asn Pro Ala 495 500 505	1836

TCC AGA CTC ACA GCA TTG AGA ATT AAG AAG ACG CTT GCC AAG ATG GTT	1884
Ser Arg Leu Thr Ala Leu Arg Ile Lys Lys Thr Leu Ala Lys Met Val	
510 515 520 525	
GAA TCC CAA GAT GTA AAA ATC TGATGGTTAA ACCATCGGAG GAGAAACTCT	1935
Glu Ser Gln Asp Val Lys Ile	
530	
AGACTGCAAG AACTGTTTT ACCCATGGCA TCGGTGGAAT TAGACTGGAA TAAGGATGTT	1995
AACTGGTTC TCAGACTCTT TCTTCCTAC GTGTTCACAG GCTGCTAATA TTAAACCTTT	2055
CAGTACTCTT ATTAGGATAC AAGCTGGAA CTTCTAAACA CTTCATTCTT TATATATGGA	2115
CAGCTTTATT TTAAATGTGG TTTTGATGC CTTTTTTAA GTGGGTTTTT ATGAACTGCA	2175
TCAAGACTTC AATCCTGATT AGTGTCTCCA GTCAAGCTCT GGGTACTGAA TTGCCTGTT	2235
ATAAAAACGGT GCTTCTGTG AAAGCCTTAA GAAGATAAAAT GAGCGCAGCA GAGATGGAGA	2295
AATAGACTTT GCCTTTACC TGAGACATTC AGTCGTTG TATTCTACCT TTGTAAAACA	2355
GCCTATAGAT GATGATGTGT TTGGGATACT GCTTATTTA TGATAGTTG TCCTGTGTCC	2415
TTAGTGATGT GTGTGTGTCT CCATGCCACAT GCACGCCGG ATTCCCTCTGC TGCCATTGAA	2475
ATTAGAAGAA AATAATTAT ATGCATGCAC AGGAAGATAT TGGTGGCCGG TGGTTTTGTG	2535
CTTAAAAAT GCAATATCTG ACCAAGATTC GCCAATCTCA TACAAGCCAT TTACTTTGCA	2595
AGTGAGATAG CTTCCCCACC AGCTTTATTT TTTAACATGA AAGCTGATGC CAAGGCCAAA	2655
AGAAGTTAA AGCATCTGTA AATTGGACT GTTTCTTC AACCAACATT TTTTTGTGG	2715
TTATTATTT TGTCACGGAA AGCATCCTCT CCAAAGTTGG AGCTTCTATT GCCATGAACC	2775
ATGCTTACAA AGAAAGCACT TCTTATTGAA GTGAATTCT GCATTTGATA GCAATGTAAG	2835
TGCCCTATAAC CATGTTCTAT ATTCTTTATT CTCAGTAACT TTTAAAAGGG AAGTTATTAA	2895
TATTTGTGT ATAATGTGCT TTATTTGCAA ATCACCC	2932

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 532 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Met Thr Gln Leu Tyr Ile Tyr Ile Arg Leu Leu Gly Ala Tyr Leu Phe	
1 5 10 15	

Ile Ile Ser Arg Val Gln Gly Gln Asn Leu Asp Ser Met Leu His Gly	
20 25 30	

Thr Gly Met Lys Ser Asp Ser Asp Gln Lys Lys Ser Glu Asn Gly Val
 35 40 45
 Thr Leu Ala Pro Glu Asp Thr Leu Pro Phe Leu Lys Cys Tyr Cys Ser
 50 55 60
 Gly His Cys Pro Asp Asp Ala Ile Asn Asn Thr Cys Ile Thr Asn Gly
 65 70 75 80
 His Cys Phe Ala Ile Ile Glu Glu Asp Asp Gln Gly Glu Thr Thr Leu
 85 90 95
 Ala Ser Gly Cys Met Lys Tyr Glu Gly Ser Asp Phe Gln Cys Lys Asp
 100 105 110
 Ser Pro Lys Ala Gln Leu Arg Arg Thr Ile Glu Cys Cys Arg Thr Asn
 115 120 125
 Leu Cys Asn Gln Tyr Leu Gln Pro Thr Leu Pro Pro Val Val Ile Gly
 130 135 140
 Pro Phe Phe Asp Gly Ser Ile Arg Trp Leu Val Leu Leu Ile Ser Met
 145 150 155 160
 Ala Val Cys Ile Ile Ala Met Ile Ile Phe Ser Ser Cys Phe Cys Tyr
 165 170 175
 Lys His Tyr Cys Lys Ser Ile Ser Ser Arg Arg Tyr Asn Arg Asp
 180 185 190
 Leu Glu Gln Asp Glu Ala Phe Ile Pro Val Gly Glu Ser Leu Lys Asp
 195 200 205
 Leu Ile Asp Gln Ser Gln Ser Ser Gly Ser Gly Ser Gly Leu Pro Leu
 210 215 220
 Leu Val Gln Arg Thr Ile Ala Lys Gln Ile Gln Met Val Arg Gln Val
 225 230 235 240
 Gly Lys Gly Arg Tyr Gly Glu Val Trp Met Gly Lys Trp Arg Gly Glu
 245 250 255
 Lys Val Ala Val Lys Val Phe Phe Thr Thr Glu Glu Ala Ser Trp Phe
 260 265 270
 Arg Glu Thr Glu Ile Tyr Gln Thr Val Leu Met Arg His Glu Asn Ile
 275 280 285
 Leu Gly Phe Ile Ala Ala Asp Ile Lys Gly Thr Gly Ser Trp Thr Gln
 290 295 300
 Leu Tyr Leu Ile Thr Asp Tyr His Glu Asn Gly Ser Leu Tyr Asp Phe
 305 310 315 320
 Leu Lys Cys Ala Thr Leu Asp Thr Arg Ala Leu Leu Lys Leu Ala Tyr
 325 330 335
 Ser Ala Ala Cys Gly Leu Cys His Leu His Thr Glu Ile Tyr Gly Thr
 340 345 350

Gln Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys Ser Lys Asn Ile
 355 360 365
 Leu Ile Lys Lys Asn Gly Ser Cys Cys Ile Ala Asp Leu Gly Leu Ala
 370 375 380
 Val Lys Phe Asn Ser Asp Thr Asn Glu Val Asp Val Pro Leu Asn Thr
 385 390 395 400
 Arg Val Gly Thr Lys Arg Tyr Met Ala Pro Glu Val Leu Asp Glu Ser
 405 410 415
 Leu Asn Lys Asn His Phe Gln Pro Tyr Ile Met Ala Asp Ile Tyr Ser
 420 425 430
 Phe Gly Leu Ile Ile Trp Glu Met Ala Arg Arg Cys Ile Thr Gly Gly
 435 440 445
 Ile Val Glu Glu Tyr Gln Leu Pro Tyr Tyr Asn Met Val Pro Ser Asp
 450 455 460
 Pro Ser Tyr Glu Asp Met Arg Glu Val Val Cys Val Lys Arg Leu Arg
 465 470 475 480
 Pro Ile Val Ser Asn Arg Trp Asn Ser Asp Glu Cys Leu Arg Ala Val
 485 490 495
 Leu Lys Leu Met Ser Glu Cys Trp Ala His Asn Pro Ala Ser Arg Leu
 500 505 510
 Thr Ala Leu Arg Ile Lys Lys Thr Leu Ala Lys Met Val Glu Ser Gln
 515 520 525
 Asp Val Lys Ile
 530

(2) INFORMATION FOR SEQ ID NO: 7:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2333 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iv) ANTI-SENSE: NO
- (v) FRAGMENT TYPE: internal
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: Homo sapiens
- (ix) FEATURE:
 - (A) NAME/KEY: CDS
 - (B) LOCATION: 1..1515

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

ATG GCG GAG TCG GCC GGA GCC TCC TCC TTC CCC CTT GTT GTC CTC Met Ala Glu Ser Ala Gly Ala Ser Ser Phe Phe Pro Leu Val Val Leu 1 5 10 15	48
CTG CTC GCC GGC AGC GGC GGG TCC GGG CCC CGG GGG GTC GCT CTG Leu Leu Ala Gly Ser Gly Ser Gly Pro Arg Gly Val Gln Ala Leu 20 25 30	96
CTG TGT GCG TGC ACC AGC TGC CTC CAG GCC AAC TAC ACG TGT GAG ACA Leu Cys Ala Cys Thr Ser Cys Leu Gln Ala Asn Tyr Thr Cys Glu Thr 35 40 45	144
GAT GGG GCC TGC ATG GTT TCC TTT TTC AAT CTG GAT GGG ATG GAG CAC Asp Gly Ala Cys Met Val Ser Phe Phe Asn Leu Asp Gly Met Glu His 50 55 60	192
CAT GTG CGC ACC TGC ATC CCC AAA GTG GAG CTG GTC CCT GCC GGG AAG His Val Arg Thr Cys Ile Pro Lys Val Glu Leu Val Pro Ala Gly Lys 65 70 75 80	240
CCC TTC TAC TGC CTG AGC TCG GAG GAC CTG CGC AAC ACC CAC TGC TGC Pro Phe Tyr Cys Leu Ser Ser Glu Asp Leu Arg Asn Thr His Cys Cys 85 90 95	288
TAC ACT GAC TAC TGC AAC AGG ATC GAC TTG AGG GTG CCC AGT GGT CAC Tyr Thr Asp Tyr Cys Asn Arg Ile Asp Leu Arg Val Pro Ser Gly His 100 105 110	336
CTC AAG CAG CCT GAG CAC CCG TCC ATG TGG GGC CCG GTG GAG CTG GTA Leu Lys Glu Pro Glu His Pro Ser Met Trp Gly Pro Val Glu Leu Val 115 120 125	384
GGC ATC ATC GCC GGC CCG GTG TTC CTC CTG TTC CTC ATC ATC ATC ATT Gly Ile Ile Ala Gly Pro Val Phe Leu Leu Phe Leu Ile Ile Ile Ile 130 135 140	432
GTG TTC CTT GTC ATT AAC TAT CAT CAG CGT GTC TAT CAC AAC CGC CAG Val Phe Leu Val Ile Asn Tyr His Gln Arg Val Tyr His Asn Arg Gln 145 150 155 160	480
AGA CTG GAC ATG GAA GAT CCC TCA TGT GAG ATG TGT CTC TCC AAA GAC Arg Leu Asp Met Glu Asp Pro Ser Cys Glu Met Cys Leu Ser Lys Asp 165 170 175	528
AAG ACG CTC CAG GAT CTT GTC TAC GAT CTC TCC ACC TCA GGG TCT GGC Lys Thr Leu Gln Asp Leu Val Tyr Asp Leu Ser Thr Ser Gly Ser Gly 180 185 190	576
TCA GGG TTA CCC CTC TTT GTC CAG CGC ACA GTG GCC CGA ACC ATC GTT Ser Gly Leu Pro Leu Phe Val Gln Arg Thr Val Ala Arg Thr Ile Val 195 200 205	624
TTA CAA GAG ATT ATT GGC AAG GGT CGG TTT GGG GAA GTA TGG CGG GGC Leu Gln Glu Ile Ile Gly Lys Gly Arg Phe Gly Glu Val Trp Arg Gly 210 215 220	672

CGC TGG AGG GGT GGT GAT GTG GCT GTG AAA ATA TTC TCT TCT CGT GAA Arg Trp Arg Gly Gly Asp Val Ala Val Lys Ile Phe Ser Ser Arg Glu 225 230 235 240	720
GAA CGG TCT TGG TTC AGG GAA GCA GAG ATA TAC CAG ACG GTC ATG CTG Glu Arg Ser Trp Phe Arg Glu Ala Glu Ile Tyr Gln Thr Val Met Leu 245 250 255	768
CGC CAT GAA AAC ATC CTT GGA TTT ATT GCT GCT GAC AAT AAA GAT AAT Arg His Glu Asn Ile Leu Gly Phe Ile Ala Ala Asp Asn Lys Asp Asn 260 265 270	816
GGC ACC TGG ACA CAG CTG TGG CTT GTT TCT GAC TAT CAT GAG CAC GGG Gly Thr Trp Thr Gln Leu Trp Leu Val Ser Asp Tyr His Glu His Gly 275 280 285	864
TCC CTG TTT GAT TAT CTG AAC CGG TAC ACA GTG ACA ATT GAG GGG ATG Ser Leu Phe Asp Tyr Leu Asn Arg Tyr Thr Val Thr Ile Glu Gly Met 290 295 300	912
ATT AAG CTG GCC TTG TCT GCT GCT AGT GGG CTG GCA CAC CTG CAC ATG Ile Lys Leu Ala Leu Ser Ala Ala Ser Gly Leu Ala His Leu His Met 305 310 315 320	960
GAG ATC GTG GGC ACC CAA GGG AAG CCT GGA ATT GCT CAT CGA GAC TTA Glu Ile Val Gly Thr Gln Gly Lys Pro Gly Ile Ala His Arg Asp Leu 325 330 335	1008
AAG TCA AAG AAC ATT CTG GTG AAG AAA AAT GGC ATG TGT GCC ATA GCA Lys Ser Lys Ile Leu Val Lys Lys Asn Gly Met Cys Ala Ile Ala 340 345 350	1056
GAC CTG GGC CTG GCT GTC CGT CAT GAT GCA GTC ACT GAC ACC ATT GAC Asp Leu Gly Leu Ala Val Arg His Asp Ala Val Thr Asp Thr Ile Asp 355 360 365	1104
ATT GCC CCG AAT CAG AGG GTG GGG ACC AAA CGA TAC ATG GCC CCT GAA Ile Ala Pro Asn Gln Arg Val Gly Thr Lys Arg Tyr Met Ala Pro Glu 370 375 380	1152
GTA CTT GAT GAA ACC ATT AAT ATG AAA CAC TTT GAC TCC TTT AAA TGT Val Leu Asp Glu Thr Ile Asn Met Lys His Phe Asp Ser Phe Lys Cys 385 390 395 400	1200
GCT GAT ATT TAT GCC CTC GGG CTT GTA TAT TGG GAG ATT GCT CGA AGA Ala Asp Ile Tyr Ala Leu Gly Leu Val Tyr Trp Glu Ile Ala Arg Arg 405 410 415	1248
TGC AAT TCT GGA GGA GTC CAT GAA GAA TAT CAG CTG CCA TAT TAC GAC Cys Asn Ser Gly Gly Val His Glu Glu Tyr Gln Leu Pro Tyr Tyr Asp 420 425 430	1296
TTA GTG CCC TCT GAC CCT TCC ATT GAG GAA ATG CGA AAG GTT GTA TGT Leu Val Pro Ser Asp Pro Ser Ile Glu Glu Met Arg Lys Val Val Cys 435 440 445	1344
GAT CAG AAG CTG CGT CCC AAC ATC CCC AAC TGG TGG CAG AGT TAT GAG Asp Gln Lys Leu Arg Pro Asn Ile Pro Asn Trp Trp Gln Ser Tyr Glu 450 455 460	1392

GCA CTG CGG GTG ATG GGG AAG ATG ATG CGA GAG TGT TGG TAT GCC AAC Ala Leu Arg Val Met Gly Lys Met Met Arg Glu Cys Trp Tyr Ala Asn 465 470 475 480	1440
GGC GCA GCC CGC CTG ACG GCC CTG CGC ATC AAG AAG ACC CTC TCC CAG Gly Ala Ala Arg Leu Thr Ala Leu Arg Ile Lys Lys Thr Leu Ser Gln 485 490 495	1488
CTC AGC GTG CAG GAA GAC GTG AAG ATC TAACTGCTCC CTCTCTCCAC Leu Ser Val Gln Glu Asp Val Lys Ile 500 505	1535
ACGGAGCTCC TGGCAGCGAG AACTACGCAC AGCTGCCGCG TTGAGCGTAC GATGGAGGCC TACCTCTCGT TTCTGCCAG CCCTCTGTGG CCAGGAGCCC TGGCCCGCAA GAGGGACAGA GCCCGGGAGA GACTCGCTCA CTCCCATGTT GGGTTTGAGA CAGACACCTT TTCTATTTAC CTCCTAATGG CATGGAGACT CTGAGAGCGA ATTGTGTGGA GAACTCAGTG CCACACCTCG AACTGGTTGT AGTGGGAAGT CCCCGAAAC CCGGTGCATC TGGCACCGTGG CCAGGAGCCA TGACAGGGGC GCTTGGGAGG GGCCGGAGGA ACCGAGGTGT TGCCAGTGCT AAGCTGCCCT GAGGGTTTCC TTGGGGACC AGCCCACAGC ACACCAAGGT GGCCCGGAAG AACAGAAGT GCAGCCCCCTC TCACAGGCAG CTCTGAGCCG CGCTTTCCCC TCCTCCCTGG GATGGACGCT GCCGGGAGAC TGCCAGTGG ACGGAATCT GCGCTTTGT CTGTCCAGCC GTGTGTGCAT GTGCCGAGGT GCCTCCCCCG TTGTGCCTGG TTCGTGCCAT GCCCTTACAC GTGCGTGTGA GTGTGTGTGT GTGTCTGTAG GTCCGCACCT ACCTGCTTGA GCTTTCTGTG CATGTGCAGG TCGGGGGTGT GGTCGTCATG CTGTCCGTGC TTGCTGGTGC CTCTTTCAAG TAGTGAGCAG CATCTAGTTT CCCTGGTGCC CTTCCCTGGA GGTCTCTCCC TCCCCCAGAG CCCCTCATGC CACAGTGGTA CTCTGTGT	1595 1655 1715 1775 1835 1895 1955 2015 2075 2135 2195 2255 2315 2333

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 505 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Met Ala Glu Ser Ala Gly Ala Ser Ser Phe Phe Pro Leu Val Val Leu
1 5 10 15

Leu Leu Ala Gly Ser Gly Ser Gly Pro Arg Gly Val Gln Ala Leu
20 25 30

Leu Cys Ala Cys Thr Ser Cys Leu Gln Ala Asn Tyr Thr Cys Glu Thr
 35 40 45

Asp Gly Ala Cys Met Val Ser Phe Phe Asn Leu Asp Gly Met Glu His
 50 55 60

His Val Arg Thr Cys Ile Pro Lys Val Glu Leu Val Pro Ala Gly Lys
 65 70 75 80

Pro Phe Tyr Cys Leu Ser Ser Glu Asp Leu Arg Asn Thr His Cys Cys
 85 90 95

Tyr Thr Asp Tyr Cys Asn Arg Ile Asp Leu Arg Val Pro Ser Gly His
 100 105 110

Leu Lys Glu Pro Glu His Pro Ser Met Trp Gly Pro Val Glu Leu Val
 115 120 125

Gly Ile Ile Ala Gly Pro Val Phe Leu Leu Phe Leu Ile Ile Ile Ile
 130 135 140

Val Phe Leu Val Ile Asn Tyr His Gln Arg Val Tyr His Asn Arg Gln
 145 150 155 160

Arg Leu Asp Met Glu Asp Pro Ser Cys Glu Met Cys Leu Ser Lys Asp
 165 170 175

Lys Thr Leu Gln Asp Leu Val Tyr Asp Leu Ser Thr Ser Gly Ser Gly
 180 185 190

Ser Gly Leu Pro Leu Phe Val Gln Arg Thr Val Ala Arg Thr Ile Val
 195 200 205

Leu Gln Glu Ile Ile Gly Lys Gly Arg Phe Gly Glu Val Trp Arg Gly
 210 215 220

Arg Trp Arg Gly Gly Asp Val Ala Val Lys Ile Phe Ser Ser Arg Glu
 225 230 235 240

Glu Arg Ser Trp Phe Arg Glu Ala Glu Ile Tyr Gln Thr Val Met Leu
 245 250 255

Arg His Glu Asn Ile Leu Gly Phe Ile Ala Ala Asp Asn Lys Asp Asn
 260 265 270

Gly Thr Trp Thr Gln Leu Trp Leu Val Ser Asp Tyr His Glu His Gly
 275 280 285

Ser Leu Phe Asp Tyr Leu Asn Arg Tyr Thr Val Thr Ile Glu Gly Met
 290 295 300

Ile Lys Leu Ala Leu Ser Ala Ala Ser Gly Leu Ala His Leu His Met
 305 310 315 320

Glu Ile Val Gly Thr Gln Gly Lys Pro Gly Ile Ala His Arg Asp Leu
 325 330 335

Lys Ser Lys Asn Ile Leu Val Lys Lys Asn Gly Met Cys Ala Ile Ala
 340 345 350

Asp Leu Gly Leu Ala Val Arg His Asp Ala Val Thr Asp Thr Ile Asp
 355 360 365
 Ile Ala Pro Asn Gln Arg Val Gly Thr Lys Arg Tyr Met Ala Pro Glu
 370 375 380
 Val Leu Asp Glu Thr Ile Asn Met Lys His Phe Asp Ser Phe Lys Cys
 385 390 395 400
 Ala Asp Ile Tyr Ala Leu Gly Leu Val Tyr Trp Glu Ile Ala Arg Arg
 405 410 415
 Cys Asn Ser Gly Gly Val His Glu Glu Tyr Gln Leu Pro Tyr Tyr Asp
 420 425 430
 Leu Val Pro Ser Asp Pro Ser Ile Glu Glu Met Arg Lys Val Val Cys
 435 440 445
 Asp Gln Lys Leu Arg Pro Asn Ile Pro Asn Trp Trp Gln Ser Tyr Glu
 450 455 460
 Ala Leu Arg Val Met Gly Lys Met Met Arg Glu Cys Trp Tyr Ala Asn
 465 470 475 480
 Gly Ala Ala Arg Leu Thr Ala Leu Arg Ile Lys Lys Thr Leu Ser Gln
 485 490 495
 Leu Ser Val Gln Glu Asp Val Lys Ile
 500 505

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2308 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: unknown
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
 (A) ORGANISM: Mouse

(ix) FEATURE:

(A) NAME/KEY: CDS
 (B) LOCATION: 77..1585

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

GGCGAGGCCGA GGTTTGCTGG GGTGAGGCAG CGGCGCGGCC GGGCCGGGCC GGGCCACAGG

60

CGCTGGCGGC GGGACC ATG GAG CGC GCG GTC GCT GCT CCG CGT CCC CGG Met Glu Ala Ala Val Ala Ala Pro Arg Pro Arg	1 5 10	109
CTG CTC CTC CTC GTG CTG GCG GCG GCG GCG GCG GCG GCG GCG GCG CTG Leu Leu Leu Leu Val Leu Ala Ala Ala Ala Ala Ala Ala Ala Leu	15 20 25	157
CTC CCG GGG GCG ACG GCG TTA CAG TGT TTC TGC CAC CTC TGT ACA AAA Leu Pro Gly Ala Thr Ala Leu Gln Cys Phe Cys His Leu Cys Thr Lys	30 35 40	205
GAC AAT TTT ACT TGT GTG ACA GAT GGG CTC TGC TTT GTC TCT GTC ACA Asp Asn Phe Thr Cys Val Thr Asp Gly Leu Cys Phe Val Ser Val Thr	45 50 55	253
GAG ACC ACA GAC AAA GTT ATA CAC AAC AGC ATG TGT ATA GCT GAA ATT Glu Thr Thr Asp Lys Val Ile His Asn Ser Met Cys Ile Ala Glu Ile	60 65 70 75	301
GAC TTA ATT CCT CGA GAT AGG CCG TTT GTA TGT GCA CCC TCT TCA AAA Asp Leu Ile Pro Arg Asp Arg Pro Phe Val Cys Ala Pro Ser Ser Lys	80 85 90	349
ACT CGG TCT GTG ACT ACA ACA TAT TGC TGC AAT CAG GAC CAT TGC AAT Thr Gly Ser Val Thr Thr Tyr Cys Cys Asn Gln Asp His Cys Asn	95 100 105	397
AAA ATA GAA CTT CCA ACT ACT GTA AAG TCA TCA CCT GGC CTT GGT CCT Lys Ile Glu Leu Pro Thr Thr Val Lys Ser Ser Pro Gly Leu Gly Pro	110 115 120	445
GTG GAA CTG CCA GCT GTC ATT GCT GGA CCA GTG TGC TTC GTC TGC ATC Val Glu Leu Ala Ala Val Ile Ala Gly Pro Val Cys Phe Val Cys Ile	125 130 135	493
TCA CTC ATG TTG ATG GTC TAT ATC TGC CAC AAC CGC ACT GTC ATT CAC Ser Leu Met Leu Met Val Tyr Ile Cys His Asn Arg Thr Val Ile His	140 145 150 155	541
CAT CGA GTG CCA AAT GAA GAG GAC CCT TCA TTA GAT CGC CCT TTT ATT His Arg Val Pro Asn Glu Glu Asp Pro Ser Leu Asp Arg Pro Phe Ile	160 165 170	589
TCA GAG GGT ACT ACG TTG AAA GAC TTA ATT TAT GAT ATG ACA ACG TCA Ser Glu Gly Thr Thr Leu Lys Asp Leu Ile Tyr Asp Met Thr Thr Ser	175 180 185	637
GGT TCT GGC TCA GGT TTA CCA TTG CTT GTT CAG AGA ACA ATT CGG AGA Gly Ser Gly Leu Pro Leu Leu Val Gln Arg Thr Ile Ala Arg	190 195 200	685
ACT ATT GTG TTA CAA GAA AGC ATT GGC AAA GGT CGA TTT GGA GAA GTT Thr Ile Val Leu Gln Glu Ser Ile Gly Lys Gly Arg Phe Gly Glu Val	205 210 215	733
TGG AGA GGA AAG TGG CGG GGA GAA GAA GTT GCT GTT AAG ATA TTC TCC Trp Arg Gly Lys Trp Arg Gly Glu Glu Val Ala Val Lys Ile Phe Ser	220 225 230 235	781

TCT AGA GAA GAA CGT TCG TGG TTC CGT GAG GCA GAG ATT TAT CAA ACT Ser Arg Glu Glu Arg Ser Trp Phe Arg Glu Ala Glu Ile Tyr Gln Thr 240 245 250	829
GTA ATG TTA CGT CAT GAA AAC ATC CTG GGA TTT ATA GCA GCA GAC AAT Val Met Leu Arg His Glu Asn Ile Leu Gly Phe Ile Ala Ala Asp Asn 255 260 265	877
AAA GAC AAT GGT ACT TGG ACT CAG CTC TGG TTG GTG TCA GAT TAT CAT Lys Asp Asn Gly Thr Trp Thr Gln Leu Trp Leu Val Ser Asp Tyr His 270 275 280	925
GAG CAT GGA TCC CTT TTT GAT TAC TTA AAC AGA TAC ACA GTT ACT GTG Glu His Gly Ser Leu Phe Asp Tyr Leu Asn Arg Tyr Thr Val Thr Val 285 290 295	973
GAA GGA ATG ATA AAA CTT GCT CTG TCC ACG GCG AGC GGT CTT GCC CAT Glu Gly Met Ile Lys Leu Ala Leu Ser Thr Ala Ser Gly Leu Ala His 300 305 310 315	1021
CTT CAC ATG GAG ATT GTT GGT ACC CAA GGA AAG CCA GCC ATT GCT CAT Leu His Met Glu Ile Val Gly Thr Gln Gly Lys Pro Ala Ile Ala His 320 325 330	1069
AGA GAT TTG AAA TCA AAG AAT ATC TTG GTA AAG AAG AAT GGA ACT TGC Arg Asp Leu Lys Ser Lys Asn Ile Leu Val Lys Lys Asn Gly Thr Cys 335 340 345	1117
TGT ATT GCA GAC TTA GGA CTG GCA GTA AGA CAT GAT TCA GCC ACA GAT Cys Ile Ala Asp Leu Gly Leu Ala Val Arg His Asp Ser Ala Thr Asp 350 355 360	1165
ACC ATT GAT ATT GCT CCA AAC CAC AGA GTG GGA ACA AAA AGG TAC ATG Thr Ile Asp Ile Ala Pro Asn His Arg Val Gly Thr Lys Arg Tyr Met 365 370 375	1213
GCC CCT GAA GTT CTC GAT GAT TCC ATA AAT ATG AAA CAT TTT GAA TCC Ala Pro Glu Val Leu Asp Asp Ser Ile Asn Met Lys His Phe Glu Ser 380 385 390 395	1261
TTC AAA CGT GCT GAC ATC TAT GCA ATG GGC TTA GTA TTC TGG GAA ATT Phe Lys Arg Ala Asp Ile Tyr Ala Met Gly Leu Val Phe Trp Glu Ile 400 405 410	1309
GCT CGA CGA TGT TCC ATT GGT GGA ATT CAT GAA GAT TAC CAA CTG CCT Ala Arg Arg Cys Ser Ile Gly Gly Ile His Glu Asp Tyr Gln Leu Pro 415 420 425	1357
TAT TAT GAT CTT GTA CCT TCT GAC CCA TCA GTT GAA GAA ATG AGA AAA Tyr Tyr Asp Leu Val Pro Ser Asp Pro Ser Val Glu Glu Met Arg Lys 430 435 440	1405
GTT GTT TGT GAA CAG AAG TTA AGG CCA AAT ATC CCA AAC AGA TGG CAG Val Val Cys Glu Gln Lys Leu Arg Pro Asn Ile Pro Asn Arg Trp Gln 445 450 455	1453
AGC TGT GAA GCC TTG AGA GTA ATG GCT AAA ATT ATG AGA GAA TGT TGG Ser Cys Glu Ala Leu Arg Val Met Ala Lys Ile Met Arg Glu Cys Trp 460 465 470 475	1501

TAT GCC AAT GGA GCA GCT AGG CTT ACA GCA TTG CGG ATT AAG AAA ACA	1549
Tyr Ala Asn Gly Ala Ala Arg Leu Thr Ala Leu Arg Ile Lys Lys Thr	
480	490
TTA TCG CAA CTC ACT CAA CAG GAA GGC ATC AAA ATG TAATTCTACA	1595
Leu Ser Gln Leu Ser Gln Gln Glu Gly Ile Lys Met	
495	500
GCTTTGCCTG AACTCTCCTT TTTCTTCAG ATCTGCTCCT GGGTTTAAT TTGGGAGGTC	1655
AGTTGTTCTA CCTCACTGAG AGGAAACAGA AGGATATTGC TTCCCTTTGC AGCAGTGTAA	1715
TAAAGTCAAT TAAAAACTTC CCAGGATTC TTTGGACCCA GGAAACAGCC ATGTGGGTCC	1775
TTTCTGTGCA CTATGAACGC TTCTTTCCCA GGACAGAAAA TGTGTAGTCT ACCTTTATT	1835
TTTATTAACA AAACTTGTTT TTTAAAAAGA TGATTGCTGG TCTTAACCTT AGGTAACCT	1895
GCTGTGCTGG AGATCATCTT TAAGGGAAA GGAGTTGGAT TGCTGAATTA CAATGAAACA	1955
TGTCTTATTA CTAAAGAAAG TGATTTACTC CTGGTTAGTA CATTCTCAGA GGATTCTGAA	2015
CCACTAGAGT TTCCCTGATT CAGACTTGA ATGTAATGTT CTATAGTTT TCAGGATCTT	2075
AAAACATAACA CTTATAAAAC TCTTATCTTG AGTCTAAAAA TGACCTCATA TAGTAGTGAG	2135
GAACATAATT CATGCAATTG TATTTTGAT ACTATTATTG TTCTTCACT TATTCAGAAC	2195
ATTACATGCC TTCAAAATGG GATTGTACTA TACCAAGTAAG TGCCACTCT GTGTCTTTCT	2255
AATGGAAATG AGTAGAATTG CTGAAAGTCT CTATGTTAAA ACCTATAGTG TTT	2308

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 503 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Met	Glu	Ala	Ala	Val	Ala	Ala	Pro	Arg	Pro	Arg	Leu	Leu	Leu	Val	
1				5				10			15				
Leu	Ala	Leu	Leu	Pro	Gly	Ala	Thr								
								20	25		30				
Ala	Leu	Gln	Cys	Phe	Cys	His	Leu	Cys	Thr	Lys	Asp	Asn	Phe	Cys	
	35						40			45					
Val	Thr	Asp	Gly	Leu	Cys	Phe	Val	Ser	Val	Thr	Glu	Thr	Thr	Asp	Lys
	50			55					60						
Val	Ile	His	Asn	Ser	Met	Cys	Ile	Ala	Glu	Ile	Asp	Leu	Ile	Pro	Arg
	65				70				75			80			

Asp Arg Pro Phe Val Cys Ala Pro Ser Ser Lys Thr Gly Ser Val Thr
 85 90 95
 Thr Thr Tyr Cys Cys Asn Gln Asp His Cys Asn Lys Ile Glu Leu Pro
 100 105 110
 Thr Thr Val Lys Ser Ser Pro Gly Leu Gly Pro Val Glu Leu Ala Ala
 115 120 125
 Val Ile Ala Gly Pro Val Cys Phe Val Cys Ile Ser Leu Met Leu Met
 130 135 140
 Val Tyr Ile Cys His Asn Arg Thr Val Ile His His Arg Val Pro Asn
 145 150 155 160
 Glu Glu Asp Pro Ser Leu Asp Arg Pro Phe Ile Ser Glu Gly Thr Thr
 165 170 175
 Leu Lys Asp Leu Ile Tyr Asp Met Thr Thr Ser Gly Ser Gly Ser Gly
 180 185 190
 Leu Pro Leu Leu Val Gln Arg Thr Ile Ala Arg Thr Ile Val Leu Gln
 195 200 205
 Glu Ser Ile Gly Lys Gly Arg Phe Gly Glu Val Trp Arg Gly Lys Trp
 210 215 220
 Arg Gly Glu Glu Val Ala Val Lys Ile Phe Ser Ser Arg Glu Glu Arg
 225 230 235 240
 Ser Trp Phe Arg Glu Ala Glu Ile Tyr Gln Thr Val Met Leu Arg His
 245 250 255
 Glu Asn Ile Leu Gly Phe Ile Ala Ala Asp Asn Lys Asp Asn Gly Thr
 260 265 270
 Trp Thr Gln Leu Trp Leu Val Ser Asp Tyr His Glu His Gly Ser Leu
 275 280 285
 Phe Asp Tyr Leu Asn Arg Tyr Thr Val Thr Val Glu Gly Met Ile Lys
 290 295 300
 Leu Ala Leu Ser Thr Ala Ser Gly Leu Ala His Leu His Met Glu Ile
 305 310 315 320
 Val Gly Thr Gln Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys Ser
 325 330 335
 Lys Asn Ile Leu Val Lys Asn Gly Thr Cys Cys Ile Ala Asp Leu
 340 345 350
 Gly Leu Ala Val Arg His Asp Ser Ala Thr Asp Thr Ile Asp Ile Ala
 355 360 365
 Pro Asn His Arg Val Gly Thr Lys Arg Tyr Met Ala Pro Glu Val Leu
 370 375 380
 Asp Asp Ser Ile Asn Met Lys His Phe Glu Ser Phe Lys Arg Ala Asp
 385 390 395 400

Ile Tyr Ala Met Gly Leu Val Phe Trp Glu Ile Ala Arg Arg Cys Ser
 405 410 415

Ile Gly Gly Ile His Glu Asp Tyr Gln Leu Pro Tyr Tyr Asp Leu Val
 420 425 430

Pro Ser Asp Pro Ser Val Glu Glu Met Arg Lys Val Val Cys Glu Gln
 435 440 445

Lys Leu Arg Pro Asn Ile Pro Asn Arg Trp Gln Ser Cys Glu Ala Leu
 450 455 460

Arg Val Met Ala Lys Ile Met Arg Glu Cys Trp Tyr Ala Asn Gly Ala
 465 470 475 480

Ala Arg Leu Thr Ala Leu Arg Ile Lys Lys Thr Leu Ser Gln Leu Ser
 485 490 495

Gln Gln Glu Gly Ile Lys Met
 500

(2) INFORMATION FOR SEQ ID NO: 11:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1922 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (v) FRAGMENT TYPE: internal
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: Mouse
- (ix) FEATURE:
 - (A) NAME/KEY: CDS
 - (B) LOCATION: 241..1746

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

GAGAGCACAG	CCCTTCCCAG	TCCCCGGAGC	CGCCGCGCCA	CGCCGGCATG	ATCAAGACCT	60
TTTCCCCGGC	CCCACAGGGC	CTCTGGACGT	GAGACCCCGG	CCGCCTCCGC	AAGGAGAGGC	120
GGGGGTGAG	TCGCCCTGTC	CAAAGGCCTC	AATCTAAACA	ATCTTGATTG	CTGTTGCCGG	180
CTGGCGGGAC	CCTGAATGGC	AGGAAATCTC	ACCACATCTC	TTCTCCTATC	TCCAAGGACC	240
ATG ACC TTG GGG AGC TTC AGA AGG GGC CTT TTG ATG CTG TCG GTG GCC						288
Met Thr Leu Gly Ser Phe Arg Arg Gly Leu Leu Met Leu Ser Val Ala						
1	5	10	15			

TTG GGC CTA ACC CAG GGG AGA CTT GCG AAG CCT TCC AAG CTG GTG AAC	336
Leu Gly Leu Thr Gln Gly Arg Leu Ala Lys Pro Ser Lys Leu Val Asn	
20 25 30	
TGC ACT TGT GAG AGC CCA CAC TGC AAG AGA CCA TTC TGC CAG GGG TCA	384
Cys Thr Cys Glu Ser Pro His Cys Lys Arg Pro Phe Cys Gln Gly Ser	
35 40 45	
TGG TGC ACA GTG GTG CTG GTT CGA GAG CAG GGC AGG CAC CCC CAG GTC	432
Trp Cys Thr Val Val Leu Val Arg Glu Gln Gly Arg His Pro Gln Val	
50 55 60	
TAT CCG GGC TGT GGG AGC CTG AAC CAG GAG CTC TGC TTG GGA CGT CCC	480
Tyr Arg Gly Cys Gly Ser Leu Asn Gln Glu Leu Cys Leu Gly Arg Pro	
65 70 75 80	
ACG GAG TTT CTG AAC CAT CAC TGC TGC TAT AGA TCC TTC TGC AAC CAC	528
Thr Glu Phe Leu Asn His His Cys Tyr Arg Ser Phe Cys Asn His	
85 90 95	
AAC GTG TCT CTG ATG CTG GAG GCC ACC CAA ACT CCT TCG GAG GAG CCA	576
Asn Val Ser Leu Met Leu Glu Ala Thr Gln Thr Pro Ser Glu Glu Pro	
100 105 110	
GAA GTT GAT GCC CAT CTG CCT CTG ATC CTG GGT CCT GTG CTG GCC TTG	624
Glu Val Asp Ala His Leu Pro Leu Ile Leu Gly Pro Val Leu Ala Leu	
115 120 125	
CCG GTC CTG GTG GCC CTG GGT GCT CTG GGC TTG TGG CGT GTC CGG CGG	672
Pro Val Leu Val Ala Leu Gly Ala Leu Gly Leu Trp Arg Val Arg Arg	
130 135 140	
AGG CAG GAG AAG CAG CGG GAT TTG CAC AGT GAC CTG GGC GAG TCC AGT	720
Arg Gln Glu Lys Gln Arg Asp Leu His Ser Asp Leu Gly Glu Ser Ser	
145 150 155 160	
CTC ATC CTG AAG GCA TCT GAA CAG GCA GAC AGC ATG TTG GGG GAC TTC	768
Leu Ile Leu Lys Ala Ser Glu Gln Ala Asp Ser Met Leu Gly Asp Phe	
165 170 175	
CTG GAC AGC GAC TGT ACC ACG GGC AGC GGC TCG GGG CTC CCC TTC TTG	816
Leu Asp Ser Asp Cys Thr Thr Gly Ser Gly Ser Gly Leu Pro Phe Leu	
180 185 190	
GTG CAG AGG ACG GTA GCT CCG CAG GTT GCG CTG GTA CAG TGT GTG GGA	864
Val Gln Arg Thr Val Ala Arg Gln Val Ala Leu Val Glu Cys Val Gly	
195 200 205	
AAG GGC CGA TAT GGC GAG GTG TGG CGC GGT TCG TGG CAT GGC GAA AGC	912
Lys Gly Arg Tyr Gly Glu Val Trp Arg Gly Ser Trp His Gly Glu Ser	
210 215 220	
GTG GCG GTC AAG ATT TTC TCC TCA CGA GAT GAG CAG TCC TGG TTC CGG	960
Val Ala Val Lys Ile Phe Ser Ser Arg Asp Glu Gln Ser Trp Phe Arg	
225 230 235 240	
GAG ACG GAG ATC TAC AAC ACA GTT CTT AGA CAC GAC AAC ATC CTA	1008
Glu Thr Glu Ile Tyr Asn Thr Val Leu Leu Arg His Asp Asn Ile Leu	
245 250 255	

GGC TTC ATC GCC TCC GAC ATG ACT TCG CGG AAC TCG AGC ACG CAG CTG Gly Phe Ile Ala Ser Asp Met Thr Ser Arg Asn Ser Ser Thr Gln Leu 260 265 270	1056
TGG CTC ATC ACC CAC TAC CAT GAA CAC GGC TCC CTC TAT GAC TTT CTG Trp Leu Ile Thr His Tyr His Glu His Gly Ser Leu Tyr Asp Phe Leu 275 280 285	1104
CAG AGG CAG ACG CTG GAG CCC CAG TTG GCC CTG AGG CTA GCT GTG TCC Gln Arg Gln Thr Leu Glu Pro Gln Leu Ala Leu Arg Leu Ala Val Ser 290 295 300	1152
CCC GCC TGC GGC CTG GCG CAC CTA CAT GTG GAG ATC TTT GGC ACT CAA Pro Ala Cys Gly Leu Ala His Leu His Val Glu Ile Phe Gly Thr Gln 305 310 315 320	1200
GGC AAA CCA GCC ATT GCC CAT CGT GAC CTC AAG AGT CGC AAT GTG CTG Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys Ser Arg Asn Val Leu 325 330 335	1248
GTC AAG AGT AAC TTG CAG TGT TGC ATT GCA GAC CTG GGA CTG GCT GTG Val Lys Ser Asn Leu Gln Cys Cys Ile Ala Asp Leu Gly Leu Ala Val 340 345 350	1296
ATG CAC TCA CAA AGC AAC GAG TAC CTG GAT ATC GGC AAC ACA CCC CGA Met His Ser Gln Ser Asn Glu Tyr Leu Asp Ile Gly Asn Thr Pro Arg 355 360 365	1344
GTG GGT ACC AAA AGA TAC ATG CCA CCC GAG GTG CTG GAT GAG CAC ATC Val Gly Thr Lys Arg Tyr Met Ala Pro Glu Val Leu Asp Glu His Ile 370 375 380	1392
CGC ACA GAC TGC TTT GAG TCG TAC AAG TGG ACA GAC ATC TGG GCC TTT Arg Thr Asp Cys Phe Glu Ser Tyr Lys Trp Thr Asp Ile Trp Ala Phe 385 390 395 400	1440
GGC CTA GTG CTA TGG GAG ATC GCC CGG CGG ACC ATC ATC AAT GGC ATT Gly Leu Val Leu Trp Glu Ile Ala Arg Arg Thr Ile Ile Asn Gly Ile 405 410 415	1488
GTG GAG GAT TAC AGG CCA CCT TTC TAT GAC ATG GTA CCC AAT GAC CCC Val Glu Asp Tyr Arg Pro Pro Phe Tyr Asp Met Val Pro Asn Asp Pro 420 425 430	1536
AGT TTT GAG GAC ATG AAA AAG GTG GTG TGC GTT GAC CAG CAG ACA CCC Ser Phe Glu Asp Met Lys Lys Val Val Cys Val Asp Gln Gln Thr Pro 435 440 445	1584
ACC ATC CCT AAC CGG CTG GCT GCA GAT CCG GTC CTC TCC GGG CTG GCC Thr Ile Pro Asn Arg Leu Ala Ala Asp Pro Val Leu Ser Gly Leu Ala 450 455 460	1632
CAG ATG ATG AGA GAG TGC TGG TAC CCC AAC CCC TCT GCT CGC CTC ACC Gln Met Met Arg Glu Cys Trp Tyr Pro Asn Pro Ser Ala Arg Leu Thr 465 470 475 480	1680
GCA CTG CGC ATA AAG AAG ACA TTG CAG AAG CTC AGT CAC AAT CCA GAG Ala Leu Arg Ile Lys Lys Thr Leu Gln Lys Leu Ser His Asn Pro Glu 485 490 495	1728

AAG CCC AAA GTG ATT CAC TAGCCCAGGG CCACCCAGGCT TCCTCTGCCT	1776
Lys Pro Lys Val Ile His	
500	
AAAGTGTGTG CTGGGGAAGA AGACATAGCC TGTCTGGGT AAGGGACTGA AGAGAGTGTG	1836
CACCGCTGCC C TGTGTGTGCC TGCTCAGCTT GCTCCAGCC CATCCAGCCA AAAATACAGC	1896
TGAGCTGAAA TTCAAAAAAA AAAAAA	1922

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 502 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Met Thr Leu Gly Ser Phe Arg Arg Gly Leu Leu Met Leu Ser Val Ala	
1 5 10 15	
Leu Gly Leu Thr Gln Gly Arg Leu Ala Lys Pro Ser Lys Leu Val Asn	
20 25 30	
Cys Thr Cys Glu Ser Pro His Cys Lys Arg Pro Phe Cys Gln Gly Ser	
35 40 45	
Trp Cys Thr Val Val Leu Val Arg Glu Gln Gly Arg His Pro Gln Val	
50 55 60	
Tyr Arg Gly Cys Gly Ser Leu Asn Gln Glu Leu Cys Leu Gly Arg Pro	
65 70 75 80	
Thr Glu Phe Leu Asn His His Cys Cys Tyr Arg Ser Phe Cys Asn His	
85 90 95	
Asn Val Ser Leu Met Leu Glu Ala Thr Gln Thr Pro Ser Glu Glu Pro	
100 105 110	
Glu Val Asp Ala His Leu Pro Leu Ile Leu Gly Pro Val Leu Ala Leu	
115 120 125	
Pro Val Leu Val Ala Leu Gly Ala Leu Gly Leu Trp Arg Val Arg Arg	
130 135 140	
Arg Gln Glu Lys Gln Arg Asp Leu His Ser Asp Leu Gly Glu Ser Ser	
145 150 155 160	
Leu Ile Leu Lys Ala Ser Glu Gln Ala Asp Ser Met Leu Gly Asp Phe	
165 170 175	
Leu Asp Ser Asp Cys Thr Thr Gly Ser Gly Ser Gly Leu Pro Phe Leu	
180 185 190	

Val Gln Arg Thr Val Ala Arg Gln Val Ala Leu Val Glu Cys Val Gly
 195 200 205
 Lys Gly Arg Tyr Gly Glu Val Trp Arg Gly Ser Trp His Gly Glu Ser
 210 215 220
 Val Ala Val Lys Ile Phe Ser Ser Arg Asp Glu Gln Ser Trp Phe Arg
 225 230 235 240
 Glu Thr Glu Ile Tyr Asn Thr Val Leu Leu Arg His Asp Asn Ile Leu
 245 250 255
 Gly Phe Ile Ala Ser Asp Met Thr Ser Arg Asn Ser Ser Thr Gln Leu
 260 265 270
 Trp Leu Ile Thr His Tyr His Glu His Gly Ser Leu Tyr Asp Phe Leu
 275 280 285
 Gln Arg Gln Thr Leu Glu Pro Gln Leu Ala Leu Arg Leu Ala Val Ser
 290 295 300
 Pro Ala Cys Gly Leu Ala His Leu His Val Glu Ile Phe Gly Thr Gln
 305 310 315 320
 Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys Ser Arg Asn Val Leu
 325 330 335
 Val Lys Ser Asn Leu Gln Cys Cys Ile Ala Asp Leu Gly Leu Ala Val
 340 345 350
 Met His Ser Gln Ser Asn Glu Tyr Leu Asp Ile Gly Asn Thr Pro Arg
 355 360 365
 Val Gly Thr Lys Arg Tyr Met Ala Pro Glu Val Leu Asp Glu His Ile
 370 375 380
 Arg Thr Asp Cys Phe Glu Ser Tyr Lys Trp Thr Asp Ile Trp Ala Phe
 385 390 395 400
 Gly Leu Val Leu Trp Glu Ile Ala Arg Arg Thr Ile Ile Asn Gly Ile
 405 410 415
 Val Glu Asp Tyr Arg Pro Pro Phe Tyr Asp Met Val Pro Asn Asp Pro
 420 425 430
 Ser Phe Glu Asp Met Lys Lys Val Val Cys Val Asp Gln Gln Thr Pro
 435 440 445
 Thr Ile Pro Asn Arg Leu Ala Ala Asp Pro Val Leu Ser Gly Leu Ala
 450 455 460
 Gln Met Met Arg Glu Cys Trp Tyr Pro Asn Pro Ser Ala Arg Leu Thr
 465 470 475 480
 Ala Leu Arg Ile Lys Lys Thr Leu Gln Lys Leu Ser His Asn Pro Glu
 485 490 495
 Lys Pro Lys Val Ile His
 500

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2070 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: unknown
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
 (A) ORGANISM: Mouse

(ix) FEATURE:

(A) NAME/KEY: CDS
 (B) LOCATION: 217..1812

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

ATTCATGAGA TCGAACATA GGTCAAAGCT GTTCGGAGAA ATTGAACTA CAGTTTTATC	60
TAGCCACATC TCTGAGAATT CTGAAGAAG CAGCAGGTGA AAGTCATTGC CAAAGTGATT	120
TGTTCTGTAA GGAAGCCTCC CTCATTCACT TACACCAGTG AGACAGCAGG ACCAGTCATT	180
CAAAGGGCCG TGTACAGGAC CGCTGGCAAT CAGACA ATG ACT CAG CTA TAC ACT	234
Met Thr Gln Leu Tyr Thr	
1 5	
TAC ATC AGA TTA CTG GGA GCC TGT CTG TTC ATC ATT TCT CAT GTT CAA	282
Tyr Ile Arg Leu Leu Gly Ala Cys Leu Phe Ile Ile Ser His Val Gln	
10 15 20	
GGG CAG AAT CTA GAT AGT ATG CTC CAT GGC ACT GGT ATG AAA TCA GAC	330
Gly Gln Asn Leu Asp Ser Met Leu His Gly Thr Gly Met Lys Ser Asp	
25 30 35	
TTG GAC CAG AAG AAG CCA GAA AAT GGA GTG ACT TTA GCA CCA GAG GAT	378
Leu Asp Gln Lys Lys Pro Glu Asn Gly Val Thr Leu Ala Pro Glu Asp	
40 45 50	
ACC TTG CCT TTC TTA AAG TGC TAT TGC TCA GGA CAC TGC CCA GAT GAT	426
Thr Leu Pro Phe Leu Lys Cys Tyr Cys Ser Gly His Cys Pro Asp Asp	
55 60 65 70	
GCT ATT AAT AAC ACA TGC ATA ACT AAT GGC CAT TGC TTT GCC ATT ATA	474
Ala Ile Asn Asn Thr Cys Ile Thr Asn Gly His Cys Phe Ala Ile Ile	
75 80 85	
GAA GAA GAT GAT CAG GGA GAA ACC ACA TTA ACT TCT GGG TGT ATG AAG	522
Glu Glu Asp Asp Gln Gly Glu Thr Thr Leu Thr Ser Gly Cys Met Lys	
90 95 100	

TAT GAA GGC TCT GAT TTT CAA TGC AAG GAT TCA CCG AAA GCC CAG CTA Tyr Glu Gly Ser Asp Phe Gln Cys Lys Asp Ser Pro Lys Ala Gln Leu 105 110 115	570
CGC AGG ACA ATA GAA TGT TGT CGG ACC AAT TTG TGC AAC CAG TAT TTG Arg Arg Thr Ile Glu Cys Cys Arg Thr Asn Leu Cys Asn Gln Tyr Leu 120 125 130	618
CAG CCT ACA CTG CCC CCT GTT ATA GGT CCG TTC TTT GAT GGC AGC Gln Pro Thr Leu Pro Pro Val Val Ile Gly Pro Phe Phe Asp Gly Ser 135 140 145 150	666
ATC CGA TGG CTG GTT GTG CTC ATT TCC ATG GCT GTC TGT ATA GTT GCT Ile Arg Trp Leu Val Val Leu Ile Ser Met Ala Val Cys Ile Val Ala 155 160 165	714
ATG ATC ATC TTC TCC AGC TGC TTT TGC TAT AAG CAT TAT TGT AAG AGT Met Ile Ile Phe Ser Ser Cys Phe Cys Tyr Lys His Tyr Cys Lys Ser 170 175 180	762
ATC TCA AGC AGG GGT CGT TAC AAC CGT GAT TTG GAA CAG GAT GAA GCA Ile Ser Ser Arg Gly Arg Tyr Asn Arg Asp Leu Glu Gln Asp Glu Ala 185 190 195	810
TTT ATT CCA GTA GGA GAA TCA TTG AAA GAC CTG ATT GAC CAG TCC CAA Phe Ile Pro Val Gly Glu Ser Leu Lys Asp Leu Ile Asp Gln Ser Gln 200 205 210	858
AGC TCT GGG AGT GGA TCT GGA TTG CCT TTA TTG GTT CAG CGA ACT ATT Ser Ser Gly Ser Gly Leu Pro Leu Leu Val Gln Arg Thr Ile 215 220 225 230	906
GCC AAA CAG ATT CAG ATG GTT CCG CAG GTT GGT AAA GGC CGC TAT GGA Ala Lys Gln Ile Gln Met Val Arg Gln Val Gly Lys Gly Arg Tyr Gly 235 240 245	954
GAA GTA TGG ATG GGT AAA TGG CGT GGT GAA AAA GTG GCT GTC AAA GTG Glu Val Trp Met Gly Lys Trp Arg Gly Glu Lys Val Ala Val Lys Val 250 255 260	1002
TTT TTT ACC ACT GAA GAA GCT AGC TGG TTT AGA GAA ACA GAA ATC TAC Phe Phe Thr Thr Glu Glu Ala Ser Trp Phe Arg Glu Thr Glu Ile Tyr 265 270 275	1050
CAG ACG GTG TTA ATG CGT CAT GAA AAT ATA CTT GGT TTT ATA GCT GCA Gln Thr Val Leu Met Arg His Glu Asn Ile Leu Gly Phe Ile Ala Ala 280 285 290	1098
GAC ATT AAA GGC ACT GGT TCC TGG ACT CAG CTG TAT TTG ATT ACT GAT Asp Ile Lys Gly Thr Gly Ser Trp Thr Gln Leu Tyr Leu Ile Thr Asp 295 300 305 310	1146
TAC CAT GAA AAT GGA TCT CTC TAT GAC TTC CTG AAA TGT GCC ACA CTA Tyr His Glu Asn Gly Ser Leu Tyr Asp Phe Leu Lys Cys Ala Thr Leu 315 320 325	1194
GAC ACC AGA GCC CTA CTC AAG TTA GCT TAT TCT GCT GCT TGT GGT CTG Asp Thr Arg Ala Leu Leu Lys Leu Ala Tyr Ser Ala Ala Cys Gly Leu 330 335 340	1242

TGC CAC CTC CAC ACA GAA ATT TAT GGT ACC CAA GGG AAG CCT GCA ATT Cys His Leu His Thr Glu Ile Tyr Gly Thr Gln Gly Lys Pro Ala Ile 345 350 355	1290
GCT CAT CGA GAC CTG AAG AGC AAA AAC ATC CTT ATT AAG AAA AAT GGA Ala His Arg Asp Leu Lys Ser Lys Asn Ile Leu Ile Lys Lys Asn Gly 360 365 370	1338
AGT TGC TGT ATT GCT GAC CTG GGC CTA GCT GTT AAA TTC AAC AGT GAT Ser Cys Cys Ile Ala Asp Leu Gly Leu Ala Val Lys Phe Asn Ser Asp 375 380 385 390	1386
ACA AAT GAA GTT GAC ATA CCC TTG AAT ACC AGG GTG GGC ACC AAG CGG Thr Asn Glu Val Asp Ile Pro Leu Asn Thr Arg Val Gly Thr Lys Arg 395 400 405	1434
TAC ATG GCT CCA GAA GTG CTG GAT GAA AGC CTG AAT AAA AAC CAT TTC Tyr Met Ala Pro Glu Val Leu Asp Glu Ser Leu Asn Lys Asn His Phe 410 415 420	1482
CAG CCC TAC ATC ATG GCT GAC ATC TAT AGC TTT GGT TTG ATC ATT TGG Gln Pro Tyr Ile Met Ala Asp Ile Tyr Ser Phe Gly Leu Ile Ile Trp 425 430 435	1530
GAA ATG GCT CGT CGT TGT ATT ACA GGA GGA ATC GTG GAG GAA TAT CAA Glu Met Ala Arg Arg Cys Ile Thr Gly Gly Ile Val Glu Glu Tyr Gln 440 445 450	1578
TTA CCA TAT TAC AAC ATG GTG CCC AGT GAC CCA TCC TAT GAG GAC ATG Leu Pro Tyr Tyr Asn Met Val Pro Ser Asp Pro Ser Tyr Glu Asp Met 455 460 465 470	1626
CGT GAG GTT GTG TGT GTG AAA CGC TTG CGG CCA ATC GTG TCT AAC CGC Arg Glu Val Val Cys Val Lys Arg Leu Arg Pro Ile Val Ser Asn Arg 475 480 485	1674
TGG AAC AGC GAT GAA TGT CTT CGA GCA GTT TTG AAG CTA ATG TCA GAA Trp Asn Ser Asp Glu Cys Leu Arg Ala Val Leu Lys Leu Met Ser Glu 490 495 500	1722
TGT TGG GCC CAT AAT CCA GCC TCC AGA CTC ACA GCT TTG AGA ATC AAG Cys Trp Ala His Asn Pro Ala Ser Arg Leu Thr Ala Leu Arg Ile Lys 505 510 515	1770
AAG ACA CTT GCA AAA ATG GTT GAA TCC CAG GAT GTA AAG ATT Lys Thr Leu Ala Lys Met Val Glu Ser Gln Asp Val Lys Ile 520 525 530	1812
TGACAATTAA ACAATTTGA GGGAGAATTT AGACTGCAAG AACTTCTTCA CCCAAGGAAT	1872
GGGTGGGATT AGCATGGAAT AGGATGTTGA CTTGGTTTCC AGACTCCTTC CTCTACATCT	1932
TCACAGGCTG CTAACAGTAA ACCTTACCGT ACTCTACAGA ATACAAGATT GGAACCTGGGA	1992
ACTTCAAACA TGTCATTCTT TATATATGAC AGCTTTGTTT TAATGTGGGG TTTTTTTGTT	2052
TGCTTTTTT GTTTTGT	2070

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 532 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Met Thr Gln Leu Tyr Thr Tyr Ile Arg Leu Leu Gly Ala Cys Leu Phe
 1 5 10 15

Ile Ile Ser His Val Gln Gly Gln Asn Leu Asp Ser Met Leu His Gly
 20 25 30

Thr Gly Met Lys Ser Asp Leu Asp Gln Lys Lys Pro Glu Asn Gly Val
 35 40 45

Thr Leu Ala Pro Glu Asp Thr Leu Pro Phe Leu Lys Cys Tyr Cys Ser
 50 55 60

Gly His Cys Pro Asp Asp Ala Ile Asn Asn Thr Cys Ile Thr Asn Gly
 65 70 75 80

His Cys Phe Ala Ile Ile Glu Glu Asp Asp Gln Gly Glu Thr Thr Leu
 85 90 95

Thr Ser Gly Cys Met Lys Tyr Glu Gly Ser Asp Phe Gln Cys Lys Asp
 100 105 110

Ser Pro Lys Ala Gln Leu Arg Arg Thr Ile Glu Cys Cys Arg Thr Asn
 115 120 125

Leu Cys Asn Gln Tyr Leu Gln Pro Thr Leu Pro Pro Val Val Ile Gly
 130 135 140

Pro Phe Phe Asp Gly Ser Ile Arg Trp Leu Val Val Leu Ile Ser Met
 145 150 155 160

Ala Val Cys Ile Val Ala Met Ile Ile Phe Ser Ser Cys Phe Cys Tyr
 165 170 175

Lys His Tyr Cys Lys Ser Ile Ser Ser Arg Gly Arg Tyr Asn Arg Asp
 180 185 190

Leu Glu Gln Asp Glu Ala Phe Ile Pro Val Gly Glu Ser Leu Lys Asp
 195 200 205

Leu Ile Asp Gln Ser Gln Ser Ser Gly Ser Gly Ser Gly Leu Pro Leu
 210 215 220

Leu Val Gln Arg Thr Ile Ala Lys Gln Ile Gln Met Val Arg Gln Val
 225 230 235 240

Gly Lys Gly Arg Tyr Gly Glu Val Trp Met Gly Lys Trp Arg Gly Glu
 245 250 255

Lys Val Ala Val Lys Val Phe Phe Thr Thr Glu Glu Ala Ser Trp Phe
 260 265 270
 Arg Glu Thr Glu Ile Tyr Gln Thr Val Leu Met Arg His Glu Asn Ile
 275 280 285
 Leu Gly Phe Ile Ala Ala Asp Ile Lys Gly Thr Gly Ser Trp Thr Gln
 290 295 300
 Leu Tyr Leu Ile Thr Asp Tyr His Glu Asn Gly Ser Leu Tyr Asp Phe
 305 310 315 320
 Leu Lys Cys Ala Thr Leu Asp Thr Arg Ala Leu Leu Lys Leu Ala Tyr
 325 330 335
 Ser Ala Ala Cys Gly Leu Cys His Leu His Thr Glu Ile Tyr Gly Thr
 340 345 350
 Gln Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys Ser Lys Asn Ile
 355 360 365
 Leu Ile Lys Lys Asn Gly Ser Cys Cys Ile Ala Asp Leu Gly Leu Ala
 370 375 380
 Val Lys Phe Asn Ser Asp Thr Asn Glu Val Asp Ile Pro Leu Asn Thr
 385 390 395 400
 Arg Val Gly Thr Lys Arg Tyr Met Ala Pro Glu Val Leu Asp Glu Ser
 405 410 415
 Leu Asn Lys Asn His Phe Gln Pro Tyr Ile Met Ala Asp Ile Tyr Ser
 420 425 430
 Phe Gly Leu Ile Ile Trp Glu Met Ala Arg Arg Cys Ile Thr Gly Gly
 435 440 445
 Ile Val Glu Glu Tyr Gln Leu Pro Tyr Tyr Asn Met Val Pro Ser Asp
 450 455 460
 Pro Ser Tyr Glu Asp Met Arg Glu Val Val Cys Val Lys Arg Leu Arg
 465 470 475 480
 Pro Ile Val Ser Asn Arg Trp Asn Ser Asp Glu Cys Leu Arg Ala Val
 485 490 495
 Leu Lys Leu Met Ser Glu Cys Trp Ala His Asn Pro Ala Ser Arg Leu
 500 505 510
 Thr Ala Leu Arg Ile Lys Lys Thr Leu Ala Lys Met Val Glu Ser Gln
 515 520 525
 Asp Val Lys Ile
 530

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2160 base pairs

(B) TYPE: nucleic acid
 (C) STRANDEDNESS: unknown
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Mouse

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 10..1524

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

CGCGGTTAC ATG GCG GAG TCG GCC GGA GCC TCC TCC TTC TTC CCC CTT	48
Met Ala Glu Ser Ala Gly Ala Ser Ser Phe Phe Pro Leu	
1 5 10	
GTT GTC CTC CTG CTC GCC GCC AGC GGC GGG TCC GGG CCC CGG GGG ATC	96
Val Val Leu Leu Leu Ala Gly Ser Gly Ser Gly Pro Arg Gly Ile	
15 20 25	
CAG GCT CTG CTG TGT GCG TGC ACC AGC TGC CTA CAG ACC AAC TAC ACC	144
Gln Ala Leu Leu Cys Ala Cys Thr Ser Cys Leu Gln Thr Asn Tyr Thr	
30 35 40 45	
TGT GAG ACA GAT GGG GCT TGC ATG GTC TCC ATC TTT AAC CTG GAT GGC	192
Cys Glu Thr Asp Gly Ala Cys Met Val Ser Ile Phe Asn Leu Asp Gly	
50 55 60	
GTC GAG CAC CAT GTA CGT ACC TGC ATC CCC AAG GTC GAG CTG GTT CCT	240
Val Glu His His Val Arg Thr Cys Ile Pro Lys Val Glu Leu Val Pro	
65 70 75	
GCT GGA AAG CCC TTC TAC TGC CTG AGT TCA GAG GAT CTG CGC AAC ACA	288
Ala Gly Lys Pro Phe Tyr Cys Leu Ser Ser Glu Asp Leu Arg Asn Thr	
80 85 90	
CAC TGC TGC TAT ATT GAC TTC TGC AAC AAG ATT GAC CTC AGG GTC CCC	336
His Cys Cys Tyr Ile Asp Phe Cys Asn Lys Ile Asp Leu Arg Val Pro	
95 100 105	
AGC GGA CAC CTC AAG GAG CCT CCG CAC CCC TCC ATG TGG GGC CCT GTG	384
Ser Gly His Leu Lys Glu Pro Ala His Pro Ser Met Trp Gly Pro Val	
110 115 120 125	
GAG CTG GTC GGC ATC ATC GCC GGC CCC GTC TTC CTC CTC TTC CTT ATC	432
Glu Leu Val Gly Ile Ile Ala Gly Pro Val Phe Leu Leu Phe Leu Ile	
130 135 140	

ATT ATC ATC GTC TTC CTG GTC ATC AAC TAT CAC CAG CGT GTC TAC CAT Ile Ile Ile Val Phe Leu Val Ile Asn Tyr His Gln Arg Val Tyr His 145 150 155	480
AAC CGC CAG AGG TTG GAC ATG GAG GAC CCC TCT TGC GAG ATG TGT CTC Asn Arg Gln Arg Leu Asp Met Glu Asp Pro Ser Cys Glu Met Cys Leu 160 165 170	528
TCC AAA GAC AAG ACG CTC CAG GAT CTC GTC TAC GAC CTC TCC ACG TCA Ser Lys Asp Lys Thr Leu Gln Asp Leu Val Tyr Asp Leu Ser Thr Ser 175 180 185	576
GGG TCT GGC TCA GGG TTA CCC CTT TTT GTC CAG CGC ACA GTG GCC CGA Gly Ser Gly Ser Gly Leu Pro Leu Phe Val Gln Arg Thr Val Ala Arg 190 195 200 205	624
ACC ATT GTT TTA CAA GAG ATT ATC GGC AAG GGC CGG TTC GGG GAA GTA Thr Ile Val Leu Gln Glu Ile Ile Gly Lys Gly Arg Phe Gly Glu Val 210 215 220	672
TGG CGT GGT CGC TGG AGG GGT GGT GAC GTG GCT GTG AAA ATC TTC TCT Trp Arg Gly Arg Trp Arg Gly Gly Asp Val Ala Val Lys Ile Phe Ser 225 230 235	720
TCT CGT GAA GAA CGG TCT TGG TTC CGT GAA GCA GAG ATC TAC CAG ACC Ser Arg Glu Glu Arg Ser Trp Phe Arg Glu Ala Glu Ile Tyr Gln Thr 240 245 250	768
GTC ATG CTG CGC CAT GAA AAC ATC CTT GGC TTT ATT GCT GCT GAC AAT Val Met Leu Arg His Glu Asn Ile Leu Gly Phe Ile Ala Ala Asp Asn 255 260 265	816
AAA GAT AAT GGC ACC TGG ACC CAG CTG TGG CTT GTC TCT GAC TAT CAC Lys Asp Asn Gly Thr Trp Thr Gln Leu Trp Leu Val Ser Asp Tyr His 270 275 280 285	864
GAG CAT GGC TCA CTG TTT GAT TAT CTG AAC CGC TAC ACA GTG ACC ATT Glu His Gly Ser Leu Phe Asp Tyr Leu Asn Arg Tyr Thr Val Thr Ile 290 295 300	912
GAG GGA ATG ATT AAG CTA GCC TTG TCT GCA GCC AGT GGT TTG GCA CAC Glu Gly Met Ile Lys Leu Ala Leu Ser Ala Ala Ser Gly Leu Ala His 305 310 315	960
CTG CAT ATG GAG ATT GTG GGC ACT CAA GGG AAG CCG GGA ATT GCT CAT Leu His Met Glu Ile Val Gly Thr Gln Gly Lys Pro Gly Ile Ala His 320 325 330	1008
CGA GAC TTG AAG TCA AAG AAC ATC CTG GTG AAA AAA AAT GGC ATG TGT Arg Asp Leu Lys Ser Lys Asn Ile Leu Val Lys Lys Asn Gly Met Cys 335 340 345	1056
GCC ATT GCA GAC CTG GGC CTG GCT GTC CGT CAT GAT GCG GTC ACT GAC Ala Ile Ala Asp Leu Gly Leu Ala Val Arg His Asp Ala Val Thr Asp 350 355 360 365	1104
ACC ATA GAC ATT GCT CCA AAT CAG AGG GTG GGG ACC AAA CGA TAC ATG Thr Ile Asp Ile Ala Pro Asn Gln Arg Val Gly Thr Lys Arg Tyr Met 370 375 380	1152

GCT CCT GAA GTC CTT GAC GAG ACA ATC AAC ATG AAG CAC TTT GAC TCC Ala Pro Glu Val Leu Asp Glu Thr Ile Asn Met Lys His Phe Asp Ser 385 390 395	1200
TTC AAA TGT GCC GAC ATC TAT GCC CTC GGG CTT GTC TAC TGG GAG ATT Phe Lys Cys Ala Asp Ile Tyr Ala Leu Gly Leu Val Tyr Trp Glu Ile 400 405 410	1248
GCA CGA AGA TGC AAT TCT GGA GGA GTC CAT GAA GAC TAT CAA CTG CCG Ala Arg Arg Cys Asn Ser Gly Gly Val His Glu Asp Tyr Gln Leu Pro 415 420 425	1296
TAT TAC GAC TTA GTG CCC TCC GAC CCT TCC ATT GAG GAG ATG CGA AAG Tyr Tyr Asp Leu Val Pro Ser Asp Pro Ser Ile Glu Glu Met Arg Lys 430 435 440 445	1344
GTT GTA TGT GAC CAG AAG CTA CGG CCC AAT GTC CCC AAC TCG TGG CAG Val Val Cys Asp Gln Lys Leu Arg Pro Asn Val Pro Asn Trp Trp Gln 450 455 460	1392
AGT TAT GAG GCC TTG CGA GTG ATG GCA AAG ATG ATG CGG GAG TGC TGG Ser Tyr Glu Ala Leu Arg Val Met Gly Lys Met Met Arg Glu Cys Trp 465 470 475	1440
TAC GCC AAT CGT GCT GCC CGT CTG ACA GCT CTG CGC ATC AAG AAG ACT Tyr Ala Asn Gly Ala Arg Leu Thr Ala Leu Arg Ile Lys Lys Thr 480 485 490	1488
CTG TCC CAG CTA AGC GTG CAG GAA GAT GTG AAG ATT TAAGCTGTT Leu Ser Gln Leu Ser Val Gln Glu Asp Val Lys Ile 495 500 505	1534
CTCTGCCTAC ACAAGAACCC TGGGCAGTGA GGATGACTGC AGCCACCGTG CAAGCGTCGT GGAGGCCTAT CCTCTTGTTT CTGCCCCGCC CTCTGGCAGA GCCCTGGCCT GCAAGAGGGA CAGAGCCTGG GAGACGGCGCG CACTCCCGTT GGGTTTGAGA CAGACACTTT TTATATTTAC CTCCTGATGG CATGGAGACC TGAGCAAATC ATGTAGTCAC TCAATGCCAC AACTCAAAC GCTTCAGTGG GAACTACAGA GACCCAGTGC ATTGCGTGTG CAGGAGCGTG AGGTGCTGGG CTCGCCAGGA GCGGCCCTTA TACCTTGTGG TCCACTGGC TGCAAGGTTTT CCTCCAGGGA CCAGTCAACT GGCATCAAGA TATTGAGAGG AACCGGAAGT TTCTCCCTCC TTCCCGTAGC AGTCCTGAGC CACACCATCC TTCTCATGGA CATCCGGAGG ACTGCCCTA GAGACACAAAC CTGCTGCCTG TCTGTCCAGC CAAGTGGCA TGTGCCAGG TGTGTCCCAC ATTGTGCCTG GTCTGTGCCA CGCCCGTGTG TGTGTGTGTG TGTGTGAGTG AGTGTGTGTG TGTACACTTA ACCTGCTTGA GCTTCTGTGC ATGTGT	1594 1654 1714 1774 1834 1894 1954 2014 2074 2134 2160

(2) INFORMATION FOR SEQ ID NO: 16:

(1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 505 amino acids

(B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Met Ala Glu Ser Ala Gly Ala Ser Ser Phe Phe Pro Leu Val Val Leu
 1 5 10 15

Leu Leu Ala Gly Ser Gly Gly Ser Gly Pro Arg Gly Ile Gln Ala Leu
 20 25 30

Leu Cys Ala Cys Thr Ser Cys Leu Gln Thr Asn Tyr Thr Cys Glu Thr
 35 40 45

Asp Gly Ala Cys Met Val Ser Ile Phe Asn Leu Asp Gly Val Glu His
 50 55 60

His Val Arg Thr Cys Ile Pro Lys Val Glu Leu Val Pro Ala Gly Lys
 65 70 75 80

Pro Phe Tyr Cys Leu Ser Ser Glu Asp Leu Arg Asn Thr His Cys Cys
 85 90 95

Tyr Ile Asp Phe Cys Asn Lys Ile Asp Leu Arg Val Pro Ser Gly His
 100 105 110

Leu Lys Glu Pro Ala His Pro Ser Met Trp Gly Pro Val Glu Leu Val
 115 120 125

Gly Ile Ile Ala Gly Pro Val Phe Leu Leu Phe Leu Ile Ile Ile
 130 135 140

Val Phe Leu Val Ile Asn Tyr His Gln Arg Val Tyr His Asn Arg Gln
 145 150 155 160

Arg Leu Asp Met Glu Asp Pro Ser Cys Glu Met Cys Leu Ser Lys Asp
 165 170 175

Lys Thr Leu Gln Asp Leu Val Tyr Asp Leu Ser Thr Ser Gly Ser Gly
 180 185 190

Ser Gly Leu Pro Leu Phe Val Gln Arg Thr Val Ala Arg Thr Ile Val
 195 200 205

Leu Gln Glu Ile Ile Gly Lys Gly Arg Phe Gly Glu Val Trp Arg Gly
 210 215 220

Arg Trp Arg Gly Gly Asp Val Ala Val Lys Ile Phe Ser Ser Arg Glu
 225 230 235 240

Glu Arg Ser Trp Phe Arg Glu Ala Glu Ile Tyr Gln Thr Val Met Leu
 245 250 255

Arg His Glu Asn Ile Leu Gly Phe Ile Ala Ala Asp Asn Lys Asp Asn
 260 265 270

Gly Thr Trp Thr Gln Leu Trp Leu Val Ser Asp Tyr His Glu His Gly
 275 280 285
 Ser Leu Phe Asp Tyr Leu Asn Arg Tyr Thr Val Thr Ile Glu Gly Met
 290 295 300
 Ile Lys Leu Ala Leu Ser Ala Ala Ser Gly Leu Ala His Leu His Met
 305 310 315 320
 Glu Ile Val Gly Thr Gln Gly Lys Pro Gly Ile Ala His Arg Asp Leu
 325 330 335
 Lys Ser Lys Asn Ile Leu Val Lys Lys Asn Gly Met Cys Ala Ile Ala
 340 345 350
 Asp Leu Gly Leu Ala Val Arg His Asp Ala Val Thr Asp Thr Ile Asp
 355 360 365
 Ile Ala Pro Asn Gln Arg Val Gly Thr Lys Arg Tyr Met Ala Pro Glu
 370 375 380
 Val Leu Asp Glu Thr Ile Asn Met Lys His Phe Asp Ser Phe Lys Cys
 385 390 395 400
 Ala Asp Ile Tyr Ala Leu Gly Leu Val Tyr Trp Glu Ile Ala Arg Arg
 405 410 415
 Cys Asn Ser Gly Gly Val His Glu Asp Tyr Gln Leu Pro Tyr Tyr Asp
 420 425 430
 Leu Val Pro Ser Asp Pro Ser Ile Glu Glu Met Arg Lys Val Val Cys
 435 440 445
 Asp Gln Lys Leu Arg Pro Asn Val Pro Asn Trp Trp Gln Ser Tyr Glu
 450 455 460
 Ala Leu Arg Val Met Gly Lys Met Met Arg Glu Cys Trp Tyr Ala Asn
 465 470 475 480
 Gly Ala Ala Arg Leu Thr Ala Leu Arg Ile Lys Lys Thr Leu Ser Gln
 485 490 495
 Leu Ser Val Gln Glu Asp Val Lys Ile
 500 505

(2) INFORMATION FOR SEQ ID NO: 17:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1952 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Mouse(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 187..1692

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

AAGCGCCGGC AGAAGTTGCC	GGCGTGGTGC	TCGTAGTGAG	GGCGCGGAGG	ACCCGGGACC	60	
TGGGAAGCGG	CGGCAGGTTA	ACTTCGGCTG	AATCACAACC	ATTTGGCGCT	GAGCTATGAC	120
AAGAGAGCAA	ACAAAAAGTT	AAAGGAGCAA	CCCGGCCATA	AGTGAAGAGA	GAAGTTTATT	180
GATAAC ATG CTC TTA CGA	AGC TCT GGA	AAA TTA	AAT GTG GGC	ACC AAG	228	
Met Leu Leu Arg	Ser Ser Gly	Lys Leu Asn Val	Gly Thr Lys			
1	5	10				
AAG GAG GAT GGA GAG	AGT ACA GCC CCC	ACC CCT CGG CCC	AAG ATC CTA		276	
Lys Glu Asp Gly Glu	Ser Thr Ala Pro	Thr Pro Arg Pro	Lys Ile Leu			
15	20	25	30			
CGT TGT AAA TGC CAC	CAC TAC TGT CCG	GAA GAC TCA GTC	AAC AAT ATC		324	
Arg Cys Lys Cys His	His Cys Pro Glu	Asp Ser Val Asn	Ile Asn Ile			
35	40	45				
TGC AGC ACA GAT GGG	TAC TGC TTC ACG	ATG ATA GAA GAA	GAT GAC TCT		372	
Cys Ser Thr Asp Gly	Tyr Cys Phe Thr	Met Ile Glu Glu	Asp Asp Ser			
50	55	60				
GGA ATG CCT GTT GTC	ACC TCT GGA TGT	CTA GGA CTA GAA	GGG TCA GAT		420	
Gly Met Pro Val Val	Thr Ser Gly Cys	Leu Gly Leu Glu	Gly Ser Asp			
65	70	75				
TTT CAA TGT CGT GAC	ACT CCC ATT CCT CAT	CAA AGA AGA	AGA TCA ATT GAA		468	
Phe Gln Cys Arg Asp	Thr Pro Ile Pro	His Gln Arg	Arg Ser Ile Glu			
80	85	90				
TGC TGC ACA GAA AGG	AAT GAG TGT AAT	AAA GAC CTC CAC	CCC ACT CTG		516	
Cys Cys Thr Glu Arg	Asn Glu Cys Asn	Lys Asp Leu His	Pro Thr Leu			
95	100	105	110			
CCT CCT CTC AAG GAC	AGA GAT TTT GTT	GAT GGG CCC ATA	CAC CAC AAG		564	
Pro Pro Leu Lys Asp	Arg Asp Phe Val	Asp Gly Pro Ile	His His Lys			
115	120	125				
GCC TTG CTT ATC TCT	GTG ACT GTC TGT	AGT TTA CTC TTG	GTC CTC ATT		612	
Ala Leu Leu Ile Ser	Val Thr Val Cys	Ser Leu Leu Val	Leu Ile			
130	135	140				
ATT TTA TTC TGT TAC	TTC AGG TAT AAA	AGA CAA GAA	GCC CGA CCT CGG		660	
Ile Leu Phe Cys Tyr	Phe Arg Tyr Lys	Arg Gln Glu	Ala Arg Pro Arg			
145	150	155				

TAC AGC ATT GCG CTG GAG CAG GAC GAG ACA TAC ATT CCT CCT GGA GAG Tyr Ser Ile Gly Leu Glu Gln Asp Glu Thr Tyr Ile Pro Pro Gly Glu 160 165 170	708
TCC CTG AGA GAC TTG ATC GAG CAG TCT CAG AGC TCG GGA AGT GGA TCA Ser Leu Arg Asp Leu Ile Glu Gln Ser Gln Ser Ser Gly Ser Gly Ser 175 180 185 190	756
GGC CTC CCT CTG CTG GTC CAA AGG ACA ATA GCT AAG CAA ATT CAG ATG Gly Leu Pro Leu Leu Val Gln Arg Thr Ile Ala Lys Gln Ile Gln Met 195 200 205	804
GTG AAG CAG ATT GGA AAA GGC CGC TAT GGC GAG GTG TGG ATG GGA AAG Val Lys Gln Ile Gly Lys Gly Arg Tyr Gly Glu Val Trp Met Gly Lys 210 215 220	852
TGG CGT GGA GAA AAG GTG GCT GTG AAA GTG TTC TTC ACC ACG GAG GAA Trp Arg Gly Glu Lys Val Ala Val Lys Val Phe Phe Thr Thr Glu Glu 225 230 235	900
GCC AGC TGG TTC CGA GAG ACT GAG ATA TAT CAG ACG GTC CTG ATG CGG Ala Ser Trp Phe Arg Glu Thr Glu Ile Tyr Gln Thr Val Leu Met Arg 240 245 250	948
CAT GAG AAT ATT CTG GGG TTC ATT GCT GCA GAT ATC AAA GGG ACT GGG His Glu Asn Ile Leu Gly Phe Ile Ala Ala Asp Ile Lys Gly Thr Gly 255 260 265 270	996
TCC TGG ACT CAG TTG TAC CTC ATC ACA GAC TAT CAT CAA AAC GGC TCC Ser Trp Thr Gln Leu Tyr Leu Ile Thr Asp Tyr His Glu Asn Gly Ser 275 280 285	1044
CTT TAT GAC TAT CTG AAA TCC ACC ACC TTA GAC GCA AAG TCC ATG CTG Leu Tyr Asp Tyr Leu Lys Ser Thr Thr Leu Asp Ala Lys Ser Met Leu 290 295 300	1092
AAG CTA GCC TAC TCC TCT GTC AGC GGC CTA TGC CAT TTA CAC ACG GAA Lys Leu Ala Tyr Ser Ser Val Ser Gly Leu Cys His Leu His Thr Glu 305 310 315	1140
ATC TTT AGC ACT CAA GGC AAG CCA GCA ATC GCC CAT CGA GAC TTG AAA Ile Phe Ser Thr Gln Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys 320 325 330	1188
AGT AAA AAC ATC CTG GTG AAG AAA AAT GGA ACT TGC TGC ATA GCA GAC Ser Lys Asn Ile Leu Val Lys Lys Asn Gly Thr Cys Cys Ile Ala Asp 335 340 345 350	1236
CTG GGC TTG GCT GTC AAG TTC ATT AGT GAC ACA AAT GAG GTT GAC ATC Leu Gly Leu Ala Val Lys Phe Ile Ser Asp Thr Asn Glu Val Asp Ile 355 360 365	1284
CCA CCC AAC ACC CGG GTT GGC ACC AAG CGC TAT ATG CCT CCA GAA GTG Pro Pro Asn Thr Arg Val Gly Thr Lys Arg Tyr Met Pro Pro Glu Val 370 375 380	1332
CTG GAC GAG AGC TTG AAT AGA AAC CAT TTC CAG TCC TAC ATT ATG GCT Leu Asp Glu Ser Leu Asn Arg Asn His Phe Gln Ser Tyr Ile Met Ala 385 390 395	1380

GAC ATG TAC AGC TTT GGA CTC ATC CTC TGG GAG ATT GCA AGG AGA TGT Asp Met Tyr Ser Phe Gly Leu Ile Leu Trp Glu Ile Ala Arg Arg Cys 400 405 410	1428
GTT TCT GGA GGT ATA GTG GAA GAA TAC CAG CTT CCC TAT CAC GAC CTG Val Ser Gly Gly Ile Val Glu Glu Tyr Gln Leu Pro Tyr His Asp Leu 415 420 425 430	1476
GTC CCC AGT GAC CCT TCT TAT GAG GAC ATG AGA GAA ATT GTG TGC ATG Val Pro Ser Asp Pro Ser Tyr Glu Asp Met Arg Glu Ile Val Cys Met 435 440 445	1524
AAG AAG TTA CGG CCT TCA TTC CCC AAT CGA TGG AGC AGT GAT GAG TGT Lys Lys Leu Arg Pro Ser Phe Pro Asn Arg Trp Ser Ser Asp Glu Cys 450 455 460	1572
CTC AGG CAG ATG GGG AAG CTT ATG ACA GAG TGC TGG GCG CAG AAT CCT Leu Arg Gln Met Gly Lys Leu Met Thr Glu Cys Trp Ala Gln Asn Pro 465 470 475	1620
GCC TCC AGG CTG ACG GCC CTG AGA GTT AAG AAA ACC CTT GCC AAA ATG Ala Ser Arg Leu Thr Ala Leu Arg Val Lys Lys Thr Leu Ala Lys Met 480 485 490	1668
TCA GAG TCC CAG GAC ATT AAA CTC TGACGTCAGA TACTTGTGGA CAGAGCAAGA Ser Glu Ser Gln Asp Ile Lys Leu 495 500	1722
ATTTCACAGA AGCATCGTTA GCCCAAGCCT TGAACGTTAG CCTACTGCC AGTGAGTTCA GACTTTCTG GAAGAGAGCA CGGTGGGCAG ACACAGAGGA ACCCAGAAAC ACGGATTCTAT CATGGCTTTC TGAGGGAGGAG AAACTGTTTG GGTAACCTGT TCAAGATATG ATGCATGTTG CTTTCTAAGA AAGCCCTGTA TTTGAAATTA CCATTTTTT ATAAAAAAA	1782 1842 1902 1952

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 502 amino acids
- (B) TYPE: amino acid
- (C) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Met Leu Leu Arg Ser Ser Gly Lys Leu Asn Val Gly Thr Lys Lys Glu 1 5 10 15
Asp Gly Glu Ser Thr Ala Pro Thr Pro Arg Pro Lys Ile Leu Arg Cys 20 25 30
Lys Cys His His Cys Pro Glu Asp Ser Val Asn Asn Ile Cys Ser 35 40 45
Thr Asp Gly Tyr Cys Phe Thr Met Ile Glu Glu Asp Asp Ser Gly Met 50 55 60

Pro Val Val Thr Ser Gly Cys Leu Gly Leu Glu Gly Ser Asp Phe Gln
 65 70 75 80

Cys Arg Asp Thr Pro Ile Pro His Gln Arg Arg Ser Ile Glu Cys Cys
 85 90 95

Thr Glu Arg Asn Glu Cys Asn Lys Asp Leu His Pro Thr Leu Pro Pro
 100 105 110

Leu Lys Asp Arg Asp Phe Val Asp Gly Pro Ile His His Lys Ala Leu
 115 120 125

Leu Ile Ser Val Thr Val Cys Ser Leu Leu Leu Val Leu Ile Ile Leu
 130 135 140

Phe Cys Tyr Phe Arg Tyr Lys Arg Gln Glu Ala Arg Pro Arg Tyr Ser
 145 150 155 160

Ile Gly Leu Glu Gln Asp Glu Thr Tyr Ile Pro Pro Gly Glu Ser Leu
 165 170 175

Arg Asp Leu Ile Glu Gln Ser Gln Ser Ser Gly Ser Gly Ser Gly Leu
 180 185 190

Pro Leu Leu Val Gln Arg Thr Ile Ala Lys Gln Ile Gln Met Val Lys
 195 200 205

Gln Ile Gly Lys Gly Arg Tyr Gly Glu Val Trp Met Gly Lys Trp Arg
 210 215 220

Gly Glu Lys Val Ala Val Lys Val Phe Phe Thr Thr Glu Glu Ala Ser
 225 230 235 240

Trp Phe Arg Glu Thr Glu Ile Tyr Gln Thr Val Leu Met Arg His Glu
 245 250 255

Asn Ile Leu Gly Phe Ile Ala Ala Asp Ile Lys Gly Thr Gly Ser Trp
 260 265 270

Thr Gln Leu Tyr Leu Ile Thr Asp Tyr His Glu Asn Gly Ser Leu Tyr
 275 280 285

Asp Tyr Leu Lys Ser Thr Thr Leu Asp Ala Lys Ser Met Leu Lys Leu
 290 295 300

Ala Tyr Ser Ser Val Ser Gly Leu Cys His Leu His Thr Glu Ile Phe
 305 310 315 320

Ser Thr Gln Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys Ser Lys
 325 330 335

Asn Ile Leu Val Lys Lys Asn Gly Thr Cys Cys Ile Ala Asp Leu Gly
 340 345 350

Leu Ala Val Lys Phe Ile Ser Asp Thr Asn Glu Val Asp Ile Pro Pro
 355 360 365

Asn Thr Arg Val Gly Thr Lys Arg Tyr Met Pro Pro Glu Val Leu Asp
 370 375 380

Glu Ser Leu Asn Arg Asn His Phe Gln Ser Tyr Ile Met Ala Asp Met
 385 390 395 400

Tyr Ser Phe Gly Leu Ile Leu Trp Glu Ile Ala Arg Arg Cys Val Ser
 405 410 415

Gly Gly Ile Val Glu Glu Tyr Gln Leu Pro Tyr His Asp Leu Val Pro
 420 425 430

Ser Asp Pro Ser Tyr Glu Asp Met Arg Glu Ile Val Cys Met Lys Lys
 435 440 445

Leu Arg Pro Ser Phe Pro Asn Arg Trp Ser Ser Asp Glu Cys Leu Arg
 450 455 460

Gln Met Gly Lys Leu Met Thr Glu Cys Trp Ala Gln Asn Pro Ala Ser
 465 470 475 480

Arg Leu Thr Ala Leu Arg Val Lys Lys Thr Leu Ala Lys Met Ser Glu
 485 490 495

Ser Gln Asp Ile Lys Leu
 500

(2) INFORMATION FOR SEQ ID NO: 19:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 28 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

GCGGATCCTG TTGTGAAGGN AATATGTG

28

(2) INFORMATION FOR SEQ ID NO: 20:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 24 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO

80

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

GCGATCCGTC CGAGTCAAAA TTTT

24

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

GCGGATCCGC GATATATTAA AAGCAA

26

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

CGGAATTCTG GTGCCATATA

20

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

ATTCAAGGGC ACATCAACTT CATTGTGTC ACTGTTG

37

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GCGGATCCAC CATGGCGGAG TCGGCC

26

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

AACACCGGGC CGGCGATGAT

20

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(iii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Gly Xaa Gly Xaa Xaa Gly
1 5

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Asp Phe Lys Ser Arg Asn
1 5

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Asp Leu Lys Ser Lys Asn
1 5

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Gly Thr Lys Arg Tyr Met
1 5

CLAIMS

1. An isolated protein having a serine/threonine kinase domain, a DFKSRN or DLKSKN sequence in subdomain VIB and/or a GTKRYM sequence in subdomain VIII.
- 5 2. A protein according to claim 1, which additionally comprises an ATP-binding sequence that is Gly-Xaa-Gly-Xaa-Xaa-Gly in subdomain I, and a Lys residue in subdomain II.
3. An isolated protein having a serine/threonine kinase domain which has more than 50% identity to the kinase 10 domain of any of the amino-acid sequences identified herein as SEQ ID. Nos. 2, 4, 6, 8, 10, 12, 14, 16 and 18.
4. A protein according to claim 3, wherein the identity is more than 60%.
5. A protein according to any preceding claim, having 15 serine/threonine kinase activity.
6. An isolated protein having all or part of any of the amino-acid sequences identified herein as SEQ. ID Nos. 2, 4, 6, 8, 10, 12, 14, 16 and 18, and activin receptor type I functionality.
- 20 7. An isolated protein having an amino-acid sequence corresponding to part or all of the amino-acid sequence of an activin type I receptor, and wherein the protein has at least one of the following characteristics:-
 - (i) serine/threonine kinase activity;
 - 25 (ii) activin-binding activity; and
 - (iii) activin type II receptor interaction.
8. An isolated protein having all or part of any of the amino-acid sequences identified herein as SEQ. ID Nos. 2, 4, 6, 8, 10, 12, 14, 16 and 18, and TGF- β -type I receptor 30 functionality.
9. An isolated protein having an amino-acid sequence corresponding to part or all of the amino-acid sequence of a TGF- β -type I receptor, and wherein the protein has at least one of the following characteristics:
 - (i) serine/threonine kinase activity;
 - (ii) TGF- β -binding activity; and
 - (iii) TGF- β -type II receptor interaction.
- 35

10. A protein according to any of claims 1 to 5, having all or part of the amino-acid sequence identified herein as SEQ ID No. 2.
11. A protein according to any of claims 1 to 7, having 5 all or part of the amino-acid sequence identified herein as SEQ ID No. 4.
12. A protein according to any of claims 1 to 5, having serine/threonine kinase activity and all or part of the amino-acid sequence identified herein as SEQ ID No. 6.
13. A protein according to any of claims 1 to 7, having 10 all or part of the amino-acid sequence identified herein as SEQ ID No. 8.
14. A protein according to any of claims 1 to 5, 8 and 9, having all or part of the amino-acid sequence identified 15 herein as SEQ ID No. 10.
15. A protein according to any of claims 1 to 5, having all or part of the amino-acid sequence identified herein as SEQ ID No. 12.
16. A protein according to any of claims 1 to 5, having 20 all or part of the amino-acid sequence identified herein as SEQ ID No. 14.
17. A protein according to any of claims 1 to 7, having all or part of the amino-acid sequence identified herein as SEQ ID No. 16.
18. A protein according to any of claims 1 to 5, having 25 all or part of the amino-acid sequence identified herein as SEQ ID No. 18.
19. A protein according to any preceding claim, that is a soluble receptor.
20. An antibody which binds specifically to a protein as 30 defined in any of claims 1 to 19 and not to at least one other such protein.
21. An isolated nucleic acid molecule which codes for, or is complementary to a nucleic acid molecule which codes 35 for, a protein as defined in any of claims 1 to 19.
22. A recombinant nucleic acid molecule comprising at least two heterologous sequences, one of which codes for,

or is complementary to a nucleic acid molecule which codes for, a protein as defined in any of claims 1 to 19.

23. A molecule according to claim 21 or claim 22, wherein the protein is a TGF- β -type I receptor.

5 24. A molecule according to claim 21 or claim 22, wherein the protein is an activin receptor.

25. A DNA or RNA/mRNA molecule according to any of claims 21 to 24.

26. A molecule according to any of claims 20 to 24, which 10 additionally comprises, operably associated with the coding sequence, a sequence adapted to allow expression of the protein.

27. A host comprising a molecule according to claim 26, which is capable of expressing the protein.

15 28. A host according to claim 27, which comprises PAE cells.

29. A host according to claim 27 or claim 28, transfected with the Chim A receptor plasmid.

30. A product according to any preceding claim, for 20 therapeutic or diagnostic use.

31. Use of a product according to any of claims 1 to 29, for the manufacture of a medicament for use in treating a condition associated with TGF activity.

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cons.aa	G 'G	G V	A K	E
hTGFBR-II	LDTLVGKGRFAEVYKARLKQNTSEQFETVAVKIFPYDHYASWKDRKDIFSDINLKHENILQF			
mActR-II B	LLEIKARGRFGCWKAQLMN-----DFVAVKIKPLQDKQSWSEREIFSTPPGMKHENILQF			
mActR-II	LLEVKARGRFGCWKAQLLN-----EVAVKIFPIQDKQSWSQNEYEVYSIPGMKHENILQF			
daf-1	LTGRVGSGRFGNVSRG DYRG-----EAVAVKVFNAIDEPAFHKEIEIFETRMLRHPNVRLY			
subdomains	I		II	III
				IV

hTGFBR-II	LTAEERRTELGKQYWLI TAFHAKGNLQEYLTRHVI SWEDLRNVGSSLARGLSHLHSDHTP-C			
mActR-II B	IAAEKRGSNLEVELWLITAFHDKGSOLIDYLGNI ITWNELCHVAETMSRGISYLHEDVPWCR			
mActR-II	IGAEKRGTSVDVWLITAFHDKGSLSDFLKANVVSWNELCHIAETMARGLAYLHEDI PGLK			
daf-1	IGSDRVDTGFVTELWLVI EYHPSGSLHDFLLENTVNIEYYNLMRSTASGLAFLHNQIGGSK			
subdomains	V			VI -A

cons.aa	DLK	N	DFG	
hTGFBR-II	-GRPKMPIVHRDLKSSNILVKNDLTCCLCDFGLSLRL---GPySSVDDLANSQVGTARYMAP			
mActR-II B	GEGHKPSIAHRDFKSKNVLLKSDLTAVLADFGЛАVRF---EPGKPPGD-THGQVGTRRYMAP			
mActR-II	-DGHKPAISHRDIKS KNVLLKNNLTACIADFGЛАLK F---EAGKSAGD-THGQVGTRRYMAP			
daf-1	-ESNKPAMAHRDIKS KNIMYKNDLTCAIGDLGLSLSKPEDAASDI IAN-ENYKCGTVRYLAP			
subdomains	VI -B		VII	VIII

Fig. 1

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a.a C C E G N M C
5' GCGGATCCTGTTGTGAAGGNAATATGTG 3' Fig. 2A
BAMHI C C G C

a.a V A V K I F
5' GCGGATCCGTCGCAGTCAAAATTT 3' Fig. 2B
BamHI G C G G C
T T T A

a.a R D I K S K N
5' GCGGATCCGCGATATTAAAAGCAA 3' Fig. 2C
BAMHI A C C GTCT
G A

a.a E P A M Y
5' CGGAATTCTGGTGCCATATA Fig. 2D
EcoRI G G G
A A

King • 3

Fig. 3 contd.

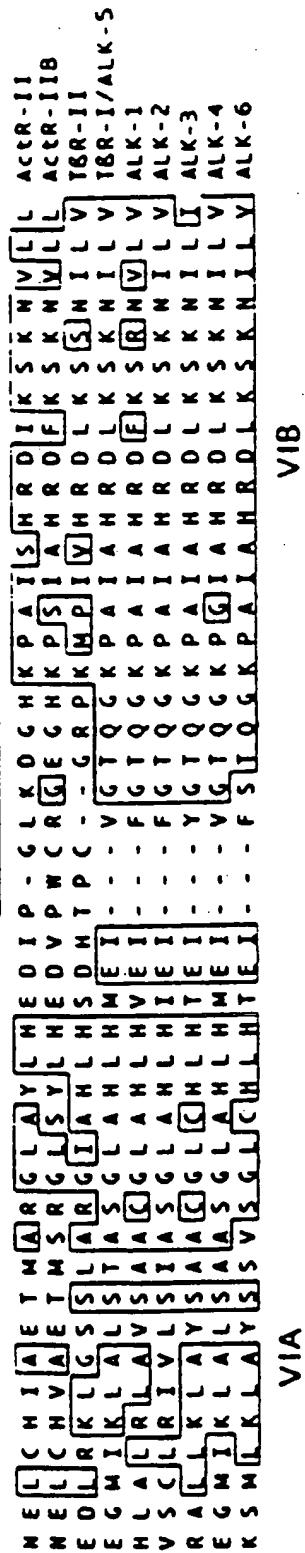
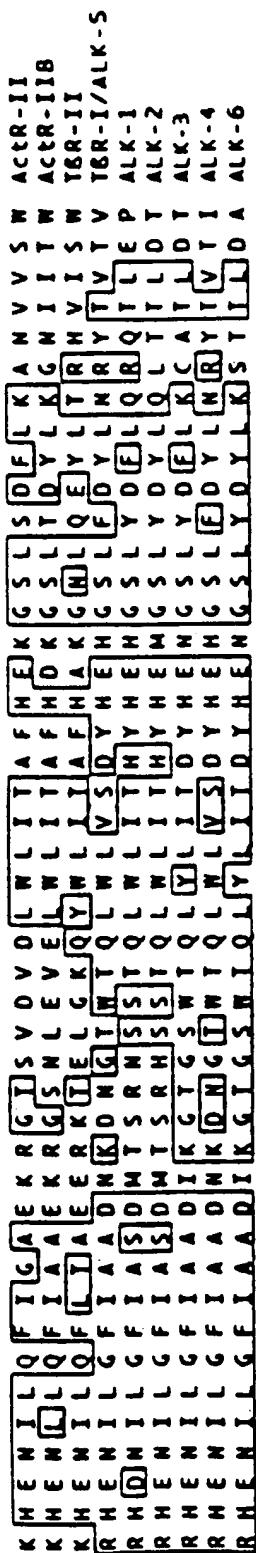
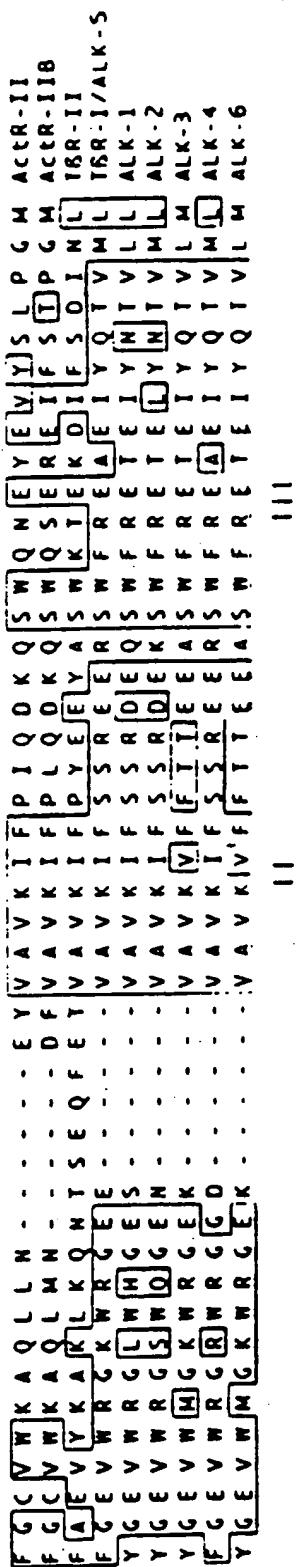


Fig. 3 contd.

VIII

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Fig. 3 contd.

P K E S S L (S13) ActR-II
P K E S S I (S36) ActR-IIIB
K (S67) Tsr-II

Fig. 3 contd.

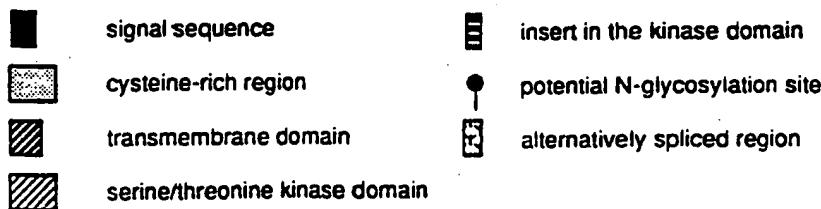
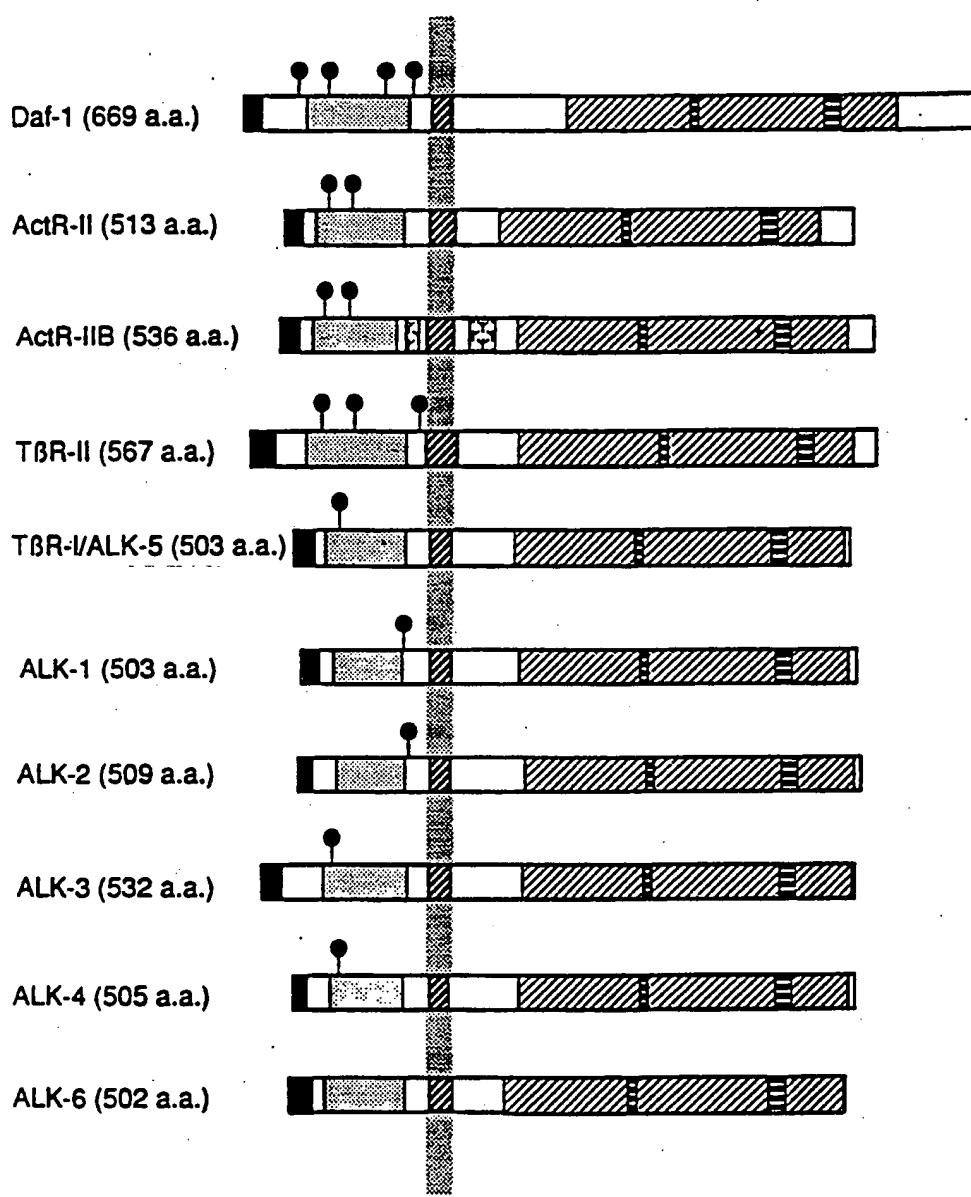


Fig. 4

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Fig. 5

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ALK-2	ALK-3	ALK-4	ALK-5	ActR-II	ActR-IIIB	T β R-II	daf-1	ALK-1
79	60	61	63	40	40	37	39	ALK-2
	63	64	65	41	39	37	39	ALK-3
		63	65	41	38	37	39	ALK-4
			90	41	40	39	42	ALK-5
				42	40	41	43	ActR-II
					78	48	35	ActR-IIIB
						47	32	T β R-II
							34	

Fig. 6

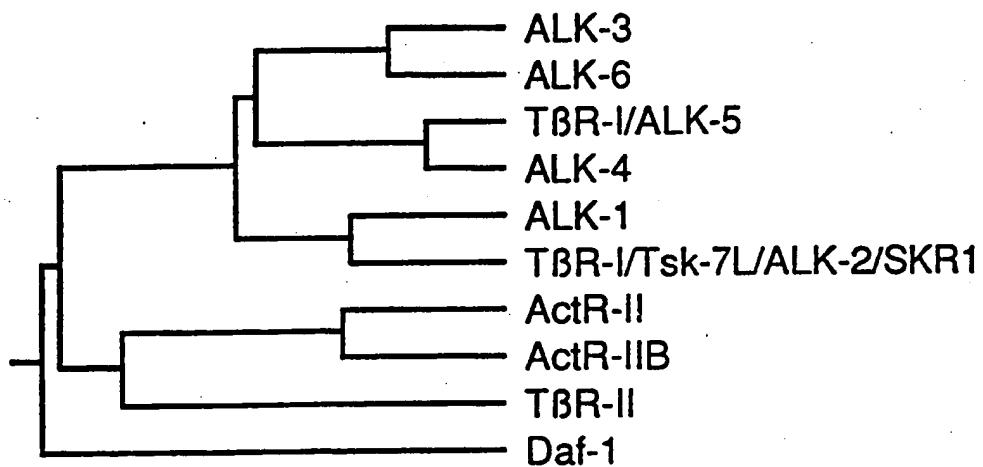


Fig. 7